VISUOSPATIAL NEGLECT AFTER STROKE

HETEROGENEITY, DIAGNOSIS AND TREATMENT

Brain Center
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Visuospatial neglect after stroke

Heterogeneity, diagnosis and treatment

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Cover	Niels van der Vaart
Layout	Teuni ten Brink
ISBN	978-94-6299-829-2

Visuospatial neglect after stroke

Heterogeneity, diagnosis and treatment

Visuospatieel neglect na beroerte
Heterogeniteit, diagnostiek en behandeling
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag
van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit
van het college voor promoties in het openbaar te verdedigen op
dinsdag 20 februari 2018 des middags te 4.15 uur

door

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geboren op 31 mei 1988
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Contents

Chapter 1

General introduction

The general objective of this thesis was to better understand and treat visuospatial neglect, a frequent and disabling disorder in lateralized attention. First, I aimed to further unravel visuospatial neglect by focusing on several subtypes. In the second part, I studied how visuospatial neglect can be measured in a more sensitive and dynamic manner. In the third part, I focused on prism adaptation as a treatment for visuospatial neglect. In particular, I evaluated the long-term effect of early treatment with prism adaptation compared to sham adaptation on neglect behaviour in daily life.

Visuospatial neglect

Visuospatial neglect (from now on “neglect” for short) is a disorder that frequently occurs following brain damage. Patients with neglect fail - or are much slower - to orient towards, respond to, and report events at one side of space (usually the side opposite to their brain lesion; the contralesional side) (Buxbaum et al., 2004; Heilman, Valenstein, & Watson, 2000). This lateralized attention deficit cannot be attributed to either motor or sensory deficits (Heilman & Valenstein, 1979). Each year, approximately 45,000 people in the Netherlands suffer from stroke (https://www.hersenstichting.nl). Of all stroke patients, 20% to 80% shows neglect (Chen, Chen, Hreha, Goedert, & Barrett, 2015). These numbers greatly vary among studies, as they depend on the specific tasks that are used, the stroke sample that is included, and the time post-stroke in which patients are assessed. In general, spontaneous neurobiological recovery of neglect takes place within the first 3 months post-stroke onset (Figure 1.1; Nijboer, Kollen, et al., 2013). In approximately 40% of patients with neglect, the disorder is still present 1 year post-stroke onset (Nijboer, Kollen, et al., 2013).

Neglect could result in several typical behaviours: patients shave only one side of their face, eat from one side of their plate, or ignore people who are located at their contralesional side. The impairment in lateralized attention is often also shown when patients are asked to draw or copy a figure (Figure 1.2). In addition, some patients do not use their contralesional limbs, even though they are physically able to. Despite these striking behaviours, patients are often not aware of the disorder or even deny it. This is the result of anosognosia (i.e., a lack of insight) which frequently co-occurs with neglect (Appelros, Karlsson, Seiger, & Nydevik, 2002).

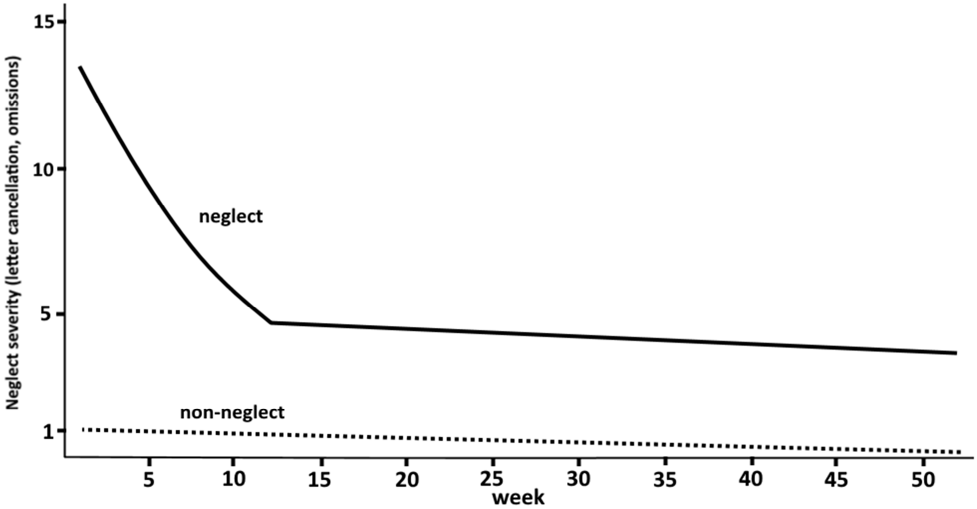


Figure 1.1 Recovery pattern of neglect as measured with a letter cancellation task. Most recovery takes place within the first 3 months post-stroke onset. Adapted from Nijboer, Kollen, & Kwakkel (2013).

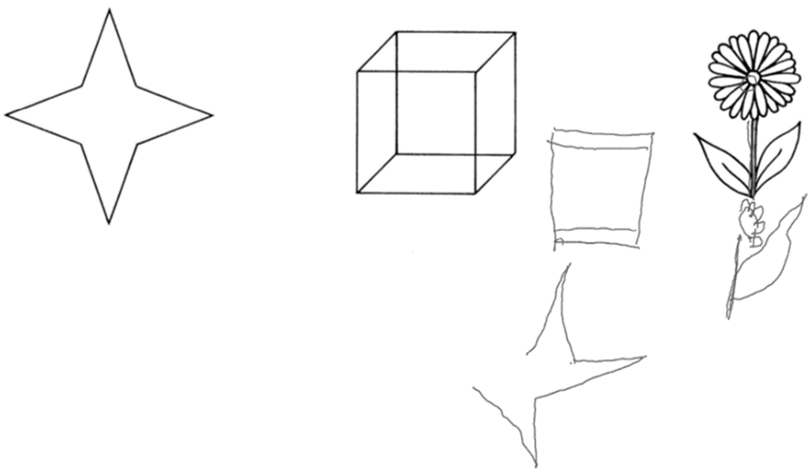


Figure 1.2 This figure shows some typical manifestations of neglect during figure copying. The upper three figures were copied by one of our participants with left-sided neglect (i.e., the lower three figures at the right side). The patient started on the right side of the workspace, copying the flower. He only copied the right side of the flower. Next, the cube was drawn, however, the three dimensions of the cube were not copied properly. Disorders in visuospatial processing are often part of neglect. Finally, the star was copied, and the left side was omitted. Note that the star was drawn on the right side of the workspace.

The clinical manifestation of neglect is often confused with cortical blindness, such as hemianopia. In both disorders, patients miss information on the affected visual field. The difference between the disorders regards their underlying mechanism. Whereas patients with hemianopia cannot *process* visual information within their affected visual field, patients with neglect do not *attend* to visual information within their affected visual field.

Neglect is associated with multiple cognitive deficits, but the core deficit is the impairment in lateralized attention. Neglect is a heterogeneous disorder, varying in sensory modality (i.e., visual, auditory and tactile; Corbetta, 2014; Jacobs, Brozzoli, & Farnè, 2012), region of space (i.e., peripersonal and extrapersonal; Aimola, Schindler, Simone, & Venneri, 2012; Van der Stoep et al., 2013), and frame of reference (i.e., egocentric and allocentric; Chechlacz et al., 2010). I will focus on *visuospatial* neglect in this thesis. Stroke patients with neglect need more help in daily life activities (ADL), such as dressing and eating, compared to patients without neglect (Nijboer, van de Port, Schepers, Post, & Visser-Meily, 2013; Nys et al., 2005). This puts a huge burden on their relatives, as they have to allocate more time to care (Chen, Fyffe, & Hreha, 2017). As a consequence, patients with neglect are less likely to being discharged home (Wee & Hopman, 2008). Furthermore, neglect has a suppressing effect on recovery in other domains as well (Buxbaum et al., 2004). For example, patients with neglect have worse motor function compared to patients without neglect and, in addition, patients with comparable motor function recover more slowly (Figure 1.3; Nijboer, Kollen, & Kwakkel, 2014; Nijboer, van de Port, et al., 2013). Eventually, patients with neglect reach a lower level of motor function compared to patients without neglect (Nijboer, Kollen, et al., 2014).

In left-sided neglect, following right brain damage, the lateralized attention deficit is generally more severe and persistent compared to right-sided neglect (see Box 1.1 for a theoretical explanation; Chen, Hreha, Kong, & Barrett, 2015; Gainotti, Messerli, & Tissot, 1972; Ogden, 1985; Ringman, Saver, Woolson, Clarke, & Adams, 2004). It is, however, unknown whether consequences in other domains are comparable between patients with left- and right-sided neglect. In **Chapter 2**, we explored which differences and similarities exist between patients with left- and right-sided neglect, regarding the severity of the lateralized attentional deficit, region specificity of neglect, cognitive functioning, physical functioning and independence in mobility and self-care. In **Chapter 3**, we evaluate how peripersonal and extrapersonal neglect differ from each other at the level of anatomy.

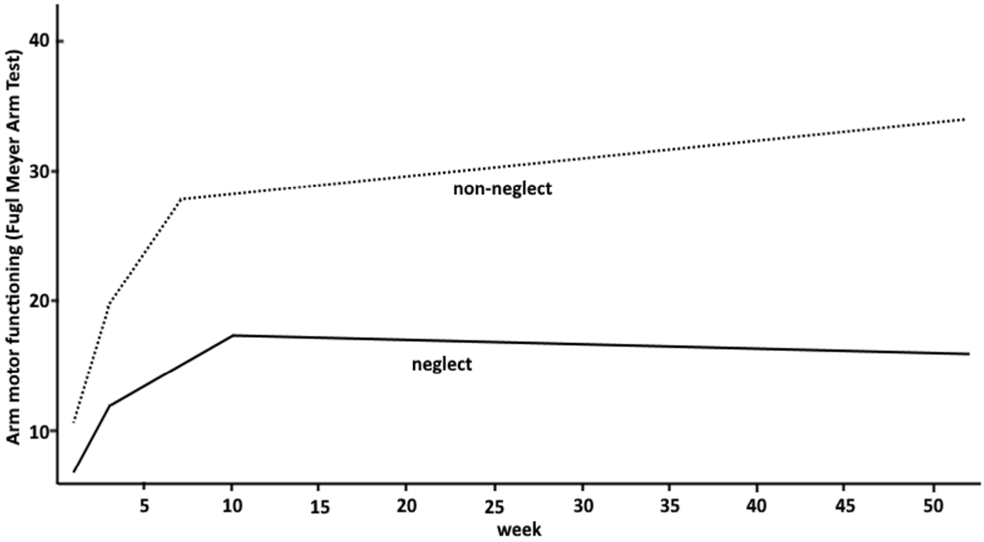


Figure 1.3 Recovery pattern of the upper limb in stroke patients with neglect (lower line) and without neglect (upper line), up to 50 weeks after stroke onset. Adapted from Nijboer, Kollen, et al. (2014).

Diagnosis

Proper diagnosis of neglect is regarded as highly important for realistic goal setting in rehabilitation and to anticipate the need for support, as patients with neglect are more dependent on their environment compared to patients without neglect (Buxbaum et al., 2004; Nijboer, van de Port, et al., 2013). In general, neuropsychological paper-and-pencil tasks, such as cancellation or bisection tasks, are used for diagnosis of neglect (Figure 1.5). Such tasks can be administered fast and easily, also in patients who are bed-bound or patients with (mild) language disorders. Sometimes, however, patients do not show neglect at these paper-and-pencil tasks, but, for example, bump into the door post just after finishing the neuropsychological assessment (Azouvi, 2017; Huisman, Visser-Meily, Eijsackers, & Nijboer, 2013; Klinke, Hjaltason, Hafsteinsdóttir, & Jónsdóttir, 2016; Ten Brink et al., 2013). This discrepancy between neglect as measured with paper-and-pencil tasks and behaviour in daily life is mostly seen in patients who have learned to use compensatory strategies. There are several explanations for this discrepancy.

Box 1.1 Right hemispherical dominance

Neglect can result from either focal cortical damage (e.g., often in the inferior parietal lobule, inferior frontal gyrus or superior temporal gyrus) or damage to white matter tracts, resulting in a disconnection of interconnected areas (Carter et al., 2017; Lunven & Bartolomeo, 2017). Visuospatial functions are not distributed symmetrically between the left and right hemispheres. The frontoparietal networks connected by the superior longitudinal fasciculus within the right hemisphere, seem particularly important for spatial attentional functions. This lateralization can be illustrated by the model of Heilman and Mesulam, in which it is stated that the left hemisphere processes information present in the right visual field, whereas the right hemisphere processes information from both the left and right visual field (Figure 1.4A; Mesulam, 1999). In the case of a lesion in the right hemisphere (Figure 1.4B), the conscious processing of information at the left side is disrupted, which results in left-sided neglect. In the case of a lesion in the left hemisphere (Figure 1.4C) (some) input at the right side is still consciously processed. Neglect will, therefore, be less frequent or less severe after a lesion in the left hemisphere compared to a lesion in the right hemisphere.

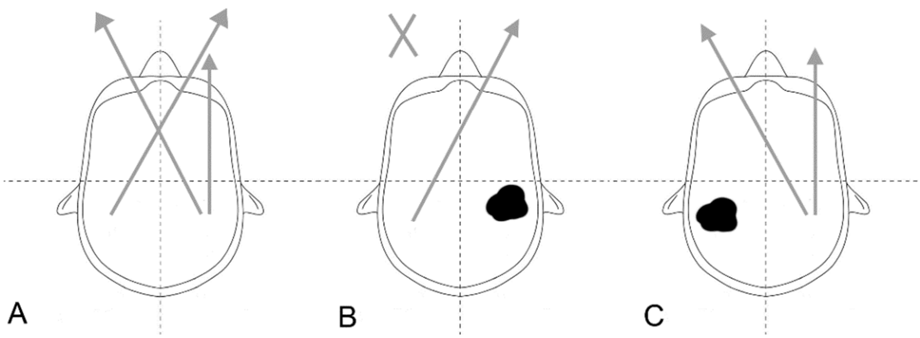


Figure 1.4 Model of attention (Mesulam, 1999). In a healthy person (A) the left hemisphere directs attention towards the right visual field, whereas the right hemisphere directs attention towards the left and right visual field. In case of a lesion in the right hemisphere (B), attention is not directed to the left. In case of a lesion in the left hemisphere (C) the right hemisphere directs (some) attention towards the right.

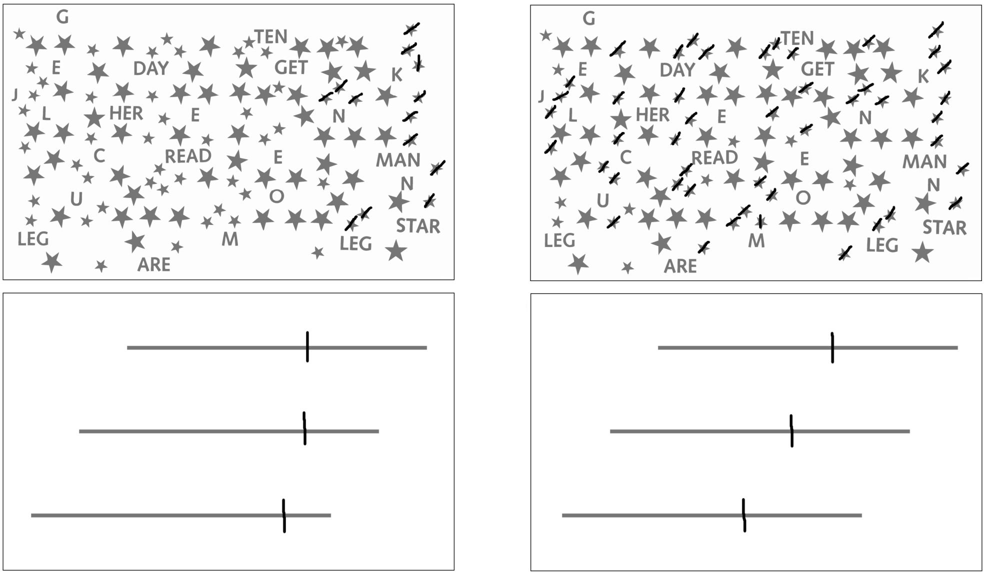


Figure 1.5 Examples of neuropsychological neglect tasks, assessed in a patient with severe neglect (left panes) and mild neglect (right panels). At the shape cancellation task (upper templates), patients are asked to mark all small stars. A difference in the number of missed stars between the left and right side of the stimulus field is used as an indication for neglect. At the line bisection task (lower templates), patients are asked to indicate the midpoint of each line. A deviation from the middle indicates neglect.

First, the aforementioned heterogeneity of neglect could underlie the dissociations found on paper-and-pencil tasks versus behaviour in daily life. Paper-and-pencil tasks are designed to objectify visual neglect in peripersonal space, thereby, other types of neglect will be missed. Second, daily life situations are more dynamic compared to the static paper-and-pencil tasks. Relevant stimuli have to be detected within a continuously moving environment, while one is also moving. When two events happen simultaneously at the ipsilesional and contralesional side, attentional competition between these events occurs. In most neglect tasks, little competition with ipsilesional stimuli exists. Finally, during paper-and-pencil tasks, patients have usually one goal to focus on. When patients have to perform several operations at the same time, such as walking, chatting and looking, the attentional capacity is limited and neglect could suddenly manifest (Chechlacz, Humphreys, & Cazzoli, 2016; Klinke et al., 2016).

In the second part of this thesis, we studied a dynamic task and several sensitive ‘dynamic measures’ of neglect. To be able to objectify neglect in a clinical setting that encompasses the dynamics of daily life, we evaluated a dynamic multitask to assess neglect in a more realistic setting: the Mobility Assessment Course (**Chapter 4**). Another approach to obtain more 'dynamic measures', is to improve analyses of behaviour as measured with existing paper-and-pencil tasks. We aimed to utilize digitized testing to extract dynamic measures from a widely used neuropsychological task for neglect assessment: a shape cancellation task. We studied measures that reflect how patients performed the cancellation task (i.e., the pattern of visual search during cancellation) instead of the final result only (i.e., the number of targets that were found eventually). In **Chapter 5**, we studied which measures can be used to depict search organization during cancellation, and whether disorganized search is related to brain damage in the right hemisphere, to neglect or both. In **Chapter 6**, we analysed the underlying neural substrates of search organization, using voxel-based lesion-symptom mapping. In **Chapter 7**, the relation between cognitive functions and search organization during cancellation was scrutinised.

Treatment

In the past century, several treatments for neglect have been developed. Currently, most guidelines for neglect treatment recommend intensive compensation training (e.g., visual scanning training) and enhancing insight, for example by means of psycho-education (e.g., see the Dutch guidelines for rehabilitation of neglect: Ten Brink, van Kessel, & Nijboer, 2017). Visual scanning training is, however, extremely time-consuming. A gap exists between the dose of visual scanning that is proposed in protocols, and the actual protocols that are used in inpatient rehabilitation environments. In addition, the top-down conscious strategies that are emphasized during visual scanning training may not be effective for all patients with neglect, as some patients have difficulties directing the head and eyes towards the instructed location (Barrett, Goedert, & Basso, 2012). It is even hypothesized that, in some patients, attention does not always accompany eye movements, thus, targets that are fixated might not reach consciousness (Khan et al., 2009). These patients might maintain attentional deficits even when they learn to make eye movements towards their neglected side, as information is not automatically attended to.

One of the most widely studied alternative treatments is prism adaptation, first described by Rossetti and colleagues (1998). Prism adaptation may be much simpler compared to visual scanning training, since it is easy to administer and conscious learning is not required, as more implicit bottom-up changes (such as an automatic recalibration of attention) are thought to occur (Saevarsson, Halsband, & Kristjansson, 2011). During the adaptation phase, patients wear goggles that produce a lateral shift of the visual field, so that targets appear displaced (Figure 1.6A). Patients can be adapted to this shift by a set of successive goal-directed visuo-motor pointing movements (Figure 1.6B). When the prisms are removed, attention is automatically recalibrated with a focus more to the contralesional side (Figure 1.6C).

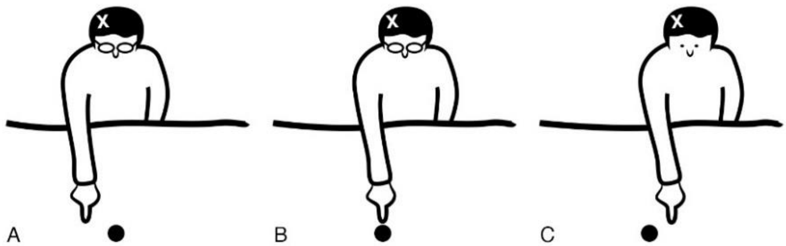


Figure 1.6 Prism adaptation session. Patients were goggles that produce a lateral shift of the visual field so that targets appear displaced (A). Patients can be adapted to this shift by a set of successive visuo-motor pointing movements (B). When the prisms are removed, attention is automatically shifted to the contralesional side (C). Figure retrieved from Ten Brink, Visser-Meily, and Nijboer (2014).

Rossetti and colleagues (1998) demonstrated a significant reduction of left-sided neglect following a brief period of prism adaptation with rightward prisms. Later studies showed that more sessions of prism adaptation (e.g., 10-20 sessions within 2-4 weeks) led to longer positive effects on neglect (Barrett et al., 2012; Champod, Frank, Taylor, & Eskes, 2016; Nijboer, Nys, van der Smagt, van der Stigchel, & Dijkerman, 2011; Yang, Zhou, Chung, Li-Tsang, & Fong, 2013). Although a reduction of neglect has been reported in various domains, not all patients benefit and not all patients improve on all neglect measures. It is unknown which specific components or sub processes of neglect are affected by prism adaptation. In a systematic review in **Chapter 8**, we evaluated specifically whether prism adaptation affects visual search in patients with neglect, and which visual search outcome measures are the most sensitive for the beneficial effects of prism adaptation.

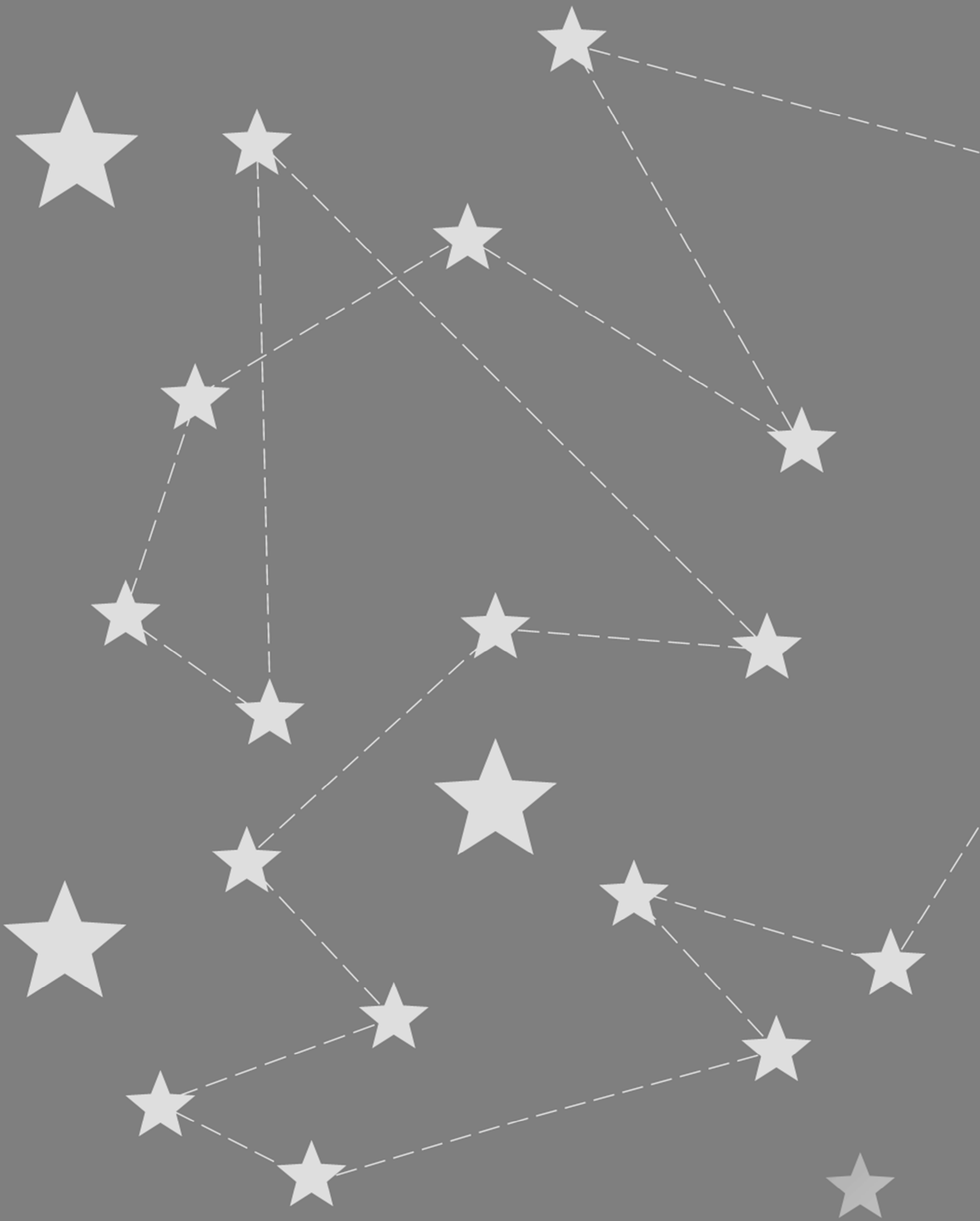
In several randomized controlled trials (RCTs), patients who received prism adaptation performed better at neuropsychological neglect tasks (Yang et al., 2013) and showed less neglect behaviour in ADL (Champod et al., 2016) compared to patients in a control group (Ten Brink, Visser-Meily, & Nijboer, 2014). However, neutral results have also been reported (Mancuso et al., 2012; Mizuno et al., 2011; Priftis, Passarini, Pilosio, Meneghello, & Pitteri, 2013; Rode et al., 2015; Spaccavento, Cellamare, Cafforio, Loverre, & Craca, 2016; Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010). Thus, results vary among studies, and notwithstanding positive results, either small groups of patients were included, measurements at the level of ADL were not always used, or follow-up measurements were not included. Furthermore, none of the studies included patients with right-sided neglect. Altogether, it is uncertain whether prism adaptation should be implemented as a rehabilitation treatment, and more evidence is needed to support this decision. In **Chapter 9** we described the protocol for the study "Prism Adaptation in Rehabilitation" (PAiR), an RCT in which early treatment with prism adaptation is compared with sham adaptation. In this chapter, inclusion and exclusion criteria are mentioned, as well as the used measures and times of administration during the study. In **Chapter 10**, the longitudinal results of the RCT PAiR are described.

Finally, **Chapter 11** is dedicated to a general discussion of the reported studies. Some highly relevant methodological issues are addressed, regarding the definition, subtypes, and diagnosis of neglect. In addition, suggestions for further research on neglect, and recommendations for clinical practice are described.

Patient population studied in this thesis

The studies described in the current thesis were performed in a distinct class of patients - namely patients admitted for inpatient rehabilitation care (10-15% of the total stroke population; van Mierlo, van Heugten, Post, de Kort, & Visser-Meily, 2015). In the Netherlands, this is a relatively young, moderately affected stroke population with potential for improvement. Although this is a selected group of stroke patients, knowledge regarding neglect in this group is highly valuable. First of all, neglect is frequently present in this population. Second, these patients eventually will go back in the society (work, social roles, etc.), and effort should be made for good recovery. Third, stroke patients are highly relevant for the rehabilitation setting, as approximately one quarter of the rehabilitation centre beds in the Netherlands are occupied by stroke patients. Finally, new diagnostic tools and treatments are eventually integrated within the current rehabilitation program, thus, should be studied in the same population.

Data was collected at De Hoogstraat Rehabilitation centre (Utrecht, The Netherlands). Within the first weeks of admission, each stroke patient was screened for neglect as part of usual care. The neglect screening consisted of several standard neuropsychological neglect tasks and some novel experimental tasks. In addition, an observation scale for neglect (i.e., the Catherine Bergego Scale) was filled in by the nurses. Data of the neglect screening was used for **Chapter 2** to **7, Chapter 9** and **Chapter 10**. Next to the neglect screening, patients were admitted to a neuropsychological assessment, and this data was used in **Chapter 7**. Finally, from August 2013 until March 2017 data was collected for the RCT PAiR (**Chapter 9** and **Chapter 10**). We included 70 stroke patients with neglect, as measured with either neuropsychological tasks or the Catherine Bergego Scale. Patients were randomized and received either prism or placebo treatment. Neglect was measured at 7 moments in time, up to 3 months post-treatment. Measures ranged from the level of function (e.g., neuropsychological tasks) to the level of ADL (e.g., Catherine Bergego Scale). To be able to study performances on relatively new tasks, such as the Mobility Assessment Course (**Chapter 4**), another 72 stroke patients without neglect, and 58 healthy control subjects were included. They were measured once.



Part I

Neglect subtypes

Chapter 2

Differences between left- and right-sided neglect revisited: A large cohort study across multiple domains

Ten Brink, A. F.*, Verwer, J. H.*, Biesbroek, J. M., Visser-Meily, J. M. A., Nijboer, T. C. W. (2017). Differences between left- and right-sided neglect revisited: A large cohort study across multiple domains. *Journal of Clinical and Experimental Neuropsychology, 39*(7), 707-723.

** The first two authors contributed equally to this work.*

Abstract

Unilateral spatial neglect (USN) is a syndrome that can occur after right- and left-hemisphere damage. It is generally accepted that left-sided USN is more severe than right-sided USN. Evidence for such a difference in other domains is lacking. Primary aims were to compare frequency, severity, region specificity, cognition, physical functioning, and physical independence between left and right USN. Secondary aims were to compare lesion characteristics. A total of 335 stroke patients admitted for inpatient rehabilitation were included. The severity of the lateralized attentional deficit was measured with a shape cancellation and line bisection test (in peripersonal and extrapersonal space) and the Catherine Bergego Scale. The Mini-Mental State Examination, Stichting Afasie Nederland score, search organization (i.e., best *r* and intersections rate), Motricity Index, balance, mobility, and self-care were assessed. Measures were statistically compared between left, right, and no USN patients. Lesion overlay plots were compared with lesion subtraction analyses. Left USN (15.8%) was more frequent than right USN (9.3%). Demographic and stroke characteristics were comparable between groups. The lateralized attentional deficit was most severe in left USN. USN in both peripersonal and extrapersonal space was more frequently left-sided in nature. Search efficiency was lower in left USN. Balance was poorer in right USN. No differences between left and right USN were found for cognitive ability, communication, motor strength, mobility, and self-care. Most patients with left USN had right-hemispheric lesions, whereas patients with right USN could have lesions in either the left or the right hemisphere. To conclude, left and right USN are both common after stroke. Although the lateralized attention deficit is worse in left than in right USN, consequences at the level of physical functioning and physical independence are largely comparable. From a clinical perspective, it is important to systematically screen for USN, both after right- and after left-hemisphere damage.

Introduction

Unilateral spatial neglect (USN) is a syndrome that occurs frequently after stroke (Appelros et al., 2002; Buxbaum et al., 2004). The core cognitive deficit of USN is a deficit in *lateralized attention*, resulting in *involuntary* impairments in detecting or responding to contralesional stimuli (Appelros et al., 2002; Buxbaum et al., 2004). Even though it is generally the lateralized inattention that is measured during, for example, a neuropsychological assessment, the most widely used term for this cognitive disorder is neglect, both in scientific studies and clinical practice. In this paper, the honoured term 'neglect' will therefore be used for sake of clarity, but one should be aware that the core deficit that we measure, and is the basis for categorizing patients, is the lateralized attention deficit. Neglect may vary in sensory modality (i.e., visual, auditory, haptic, and tactile; Jacobs et al., 2012), region of space (i.e., peripersonal and extrapersonal; Van der Stoep et al., 2013), and frame of reference (i.e., egocentric and allocentric; Chechlacz et al., 2010). Spontaneous recovery of USN takes place within the first 3 months post-stroke onset, leaving about 40% of neglect patients with chronic USN after 1 year post-stroke onset (Nijboer, Kollen, et al., 2013; Ringman et al., 2004).

Estimations are that USN occurs in approximately 50% of stroke patients with right-sided hemisphere damage and in 30% of stroke patients with left-sided hemisphere damage (Chen, Chen, et al., 2015). Some studies report that USN is more severe and more persistent after right hemisphere damage compared to left hemisphere damage (Chen, Hreha, et al., 2015; Gainotti et al., 1972; Ogden, 1985; Ringman et al., 2004), whereas others indicate that USN severity does not differ between left and right USN (Chen, Chen, et al., 2015; Suchan, Rorden, & Karnath, 2012). This right hemispheric dominance of USN has not yet been completely elucidated. A widely accepted theory of USN states that the right hemisphere controls shifts of attention to both the left and right side of space, while the left hemisphere only controls attention to the right side (Mesulam, 1981). Another theory proposes that both hemispheres have a role in orienting to the contralesional side, but this bias is larger in the left than right hemisphere (Kinsbourne, 1987). Corbetta and Shulman (2011) propose that lesions in right hemisphere ventral regions would result in a disturbed balance between hemispheres regarding physiological activity, resulting in a left-hemispheric dominance. Both theories, however, have received limited empirical support from neuroimaging studies. The non-spatial functions of the ventral attention network, such as reorienting, target detection, visual search, and arousal, are strongly right-hemisphere dominant (Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Ten Brink, Biesbroek, et al., 2016).

In general, USN is linked to poor motor recovery (Nijboer, Kollen, et al., 2014), higher disability (Appelros et al., 2002; Buxbaum et al., 2004; Chen, Chen, et al., 2015; Nijboer, van de Port, et al., 2013), poor responses to rehabilitation services (Chen, Chen, et al., 2015; Chen, Hreha, et al., 2015; Nys et al., 2005), and a reduced likelihood to being discharged home (Wee & Hopman, 2008). More severe USN is associated with more suppression on the (pattern of) recovery in other domains (Nijboer, Kollen, et al., 2014); however, it is unknown whether a difference between the left and right networks exist. In none of the studies was a dissociation between left and right brain-damaged patients, or left and right USN, made (Appelros et al., 2002; Buxbaum et al., 2004; Chen, Chen, et al., 2015; Chen, Hreha, et al., 2015; Nijboer, Kollen, et al., 2014; Nijboer, van de Port, et al., 2013; Nys et al., 2005). Since USN is thought to be more severe after right- than after left-hemispherical damage, possibly, motor, functional or cognitive differences exist too between left and right USN patients.

The primary aim of the current study was to investigate the distinctions and similarities between patients with left and right USN in a large cohort of stroke patients, regarding frequency, severity, and region-specific USN (i.e., peripersonal, extrapersonal), cognition, physical functioning, and physical independence. The secondary aim was to compare lesion characteristics between patients with left versus right USN. To our knowledge, we are the first to assess all these different domains to compare performance between left, right, and no USN groups.

Methods

Patients

Stroke patients were included from a patient population admitted for inpatient rehabilitation to De Hoogstraat Rehabilitation centre, from October 2011 to August 2014. In the Netherlands, a patient is admitted to a rehabilitation centre if (a) discharge to home is expected in view of the prognosis and availability of the caregivers, but not from the hospital within 5 days; (b) the patient is capable of participating in therapy; (c) the patient is vital enough; (d) a multidisciplinary approach is essential to reach the complex rehabilitation goals; and (e) discharge to home is expected to be within 3 months. Older patients (75 years or older) are more likely to be admitted to geriatric rehabilitation.

All stroke patients were screened for USN as part of standard care, within 2 weeks after admission. From the resulting database, the following exclusion criteria were used for the current study: (a) not screened for USN (due to being sick, being absent, or a lack of motivation); (b) not able to perform the object cancellation task (i.e., unable to understand instructions, unable to use a computer mouse, or severe alterations in vision); (c) performed the object cancellation task in only one region of space (due to fatigue, lack of motivation, or lack of time); (d) absence of data on hemisphere of lesion; and (e) discrepancy regarding side of USN between peripersonal and extrapersonal space.

Patients were grouped based on the presence of a deficit in lateralized attention. Performance at the object cancellation was used to group patients (see *Severity of the lateralized attentional deficit).* An omission difference score (left versus right) of at least 2 was used as the criterion for USN (Van der Stoep et al., 2013). Subsequently, patients with a lateralized attentional deficit were allocated to the "left USN" or "right USN" group, exclusively based on the laterality of omissions on the object cancellation task. Patients with a lateralized attentional deficit in peripersonal and/or extrapersonal space were classified as either left or right USN. Patients without a lateralized attentional deficit formed the third group (i.e., no USN). Lesion side was not taken into account in the allocation procedure.

Procedure

The data was collected from existing databases (Supplementary Table 2.1). We collected demographic and stroke characteristics, measures of communication, overall cognition, and physical independence from patient files, and lesion characteristics from magnetic resonance imaging (MRI) or computed tomography (CT) scans. Within 2 weeks after admission, a neuropsychologist conducted a USN screening (consisting of the object cancellation task and line bisection task) and administered measurements of balance for all stroke patients. Within the same week, the nurse observed the presence and severity of USN during activities of daily living (ADL) with the Catherine Bergego Scale (CBS). The research and consent procedures were in accordance with the standards of the Declaration of Helsinki.

Outcome measures

Outcomes split for left and right USN are presented per domain. The domains are: severity of the lateralized attentional deficit, other cognitive measures, and physical functioning and physical independence for the primary aims, and lesion characteristics for the secondary aims.

Severity of the lateralized attentional deficit

A digitized object cancellation task was performed both in peripersonal and in extrapersonal space (Van der Stoep et al., 2013). Object cancellation tasks are the most widely used and most valid task to assess USN (Machner, Mah, Gorgoraptis, & Husain, 2012; Sperber & Karnath, 2016). The object cancellation task consisted of 54 small objects (0.6° x 0.6°) among 75 distractors (identical, yet larger objects 0.95° x 0.95°) and letters and letter combinations (0.45° x 2.1°). Patients were seated in front of a monitor and used a computer mouse to click at the targets. Patients were instructed to indicate when they were finished. After each click, a blue circle appeared on the clicked location and remained visible throughout the task. There was no time limit. The monitor was placed at a distance of 30 cm for assessing peripersonal USN, and at a distance of 120 cm for assessing extrapersonal USN. Stimuli in extrapersonal space were presented enlarged to control for visual angle. The order of the region-specific measurements (peripersonal and extrapersonal) was randomized across patients.

The following outcome measures were derived: omission difference score, centre of cancellation (CoC), consistency of the search direction (best *r*), and intersections rate. Best *r* and the intersections rate are measures of search organization, and are described in “Other cognitive measures”. The horizontal normalized CoC (CoC-x) reflects both the location and amount of the cancelled targets (Rorden & Karnath, 2010). The CoC-x ranges from -1 to 1. For example, a missed target at the most left side of the stimulus field results in a shift of the CoC-x towards 1, reflecting a CoC towards the right side. A CoC-x of zero indicates an absence of a spatial bias regarding the cancelled targets. The CoC-x outcome was used to determine the severity of deficit in lateralized attention. Since left USN would result in a positive CoC-x, and right USN would result in a negative CoC-x, differences between relative CoC-x values would not be informative. Therefore, to compare the left and right USN group, the absolute values of the CoC-x were used.

A digitized line bisection task was administered in peripersonal and extrapersonal space, in which the same distances were used as in the object cancellation task (Van der Stoep et al., 2013). Three horizontal lines (22° long and 0.2° thick) were presented at different horizontal positions. From upper to lower lines, the horizontal shift was always 15% of the line length to the left. The lines were vertically evenly distributed: the vertical shift was 28% of the line length. Patients were asked to mark the subjective midpoint of each line by clicking on it with a computer mouse. Patients were instructed to start with the upper line. The task was conducted four times, resulting in bisecting a total of 12 lines. Scoring was conducted according the method of Van der Stoep et al. (2013): a negative value reflects a shift of the subjective midpoint to the left, and a positive value vice versa. The normal range (mean ±3 *SD*) was -0.74° to 0.48° for the presented lines in peripersonal space and -0.86° to 0.56° for the presented lines in extrapersonal space (Van der Stoep et al., 2013). For each region of space the average deviation for all lines (upper, middle and bottom) was used as an outcome measure for the severity of the deficit in lateralized attention. For evaluation of both the direction of deviation (i.e., side of USN) and the degree of deviation (i.e., severity of deficit in lateralized attention) both relative and absolute values of the averaged deviation scores were used.

The CBS is an observation scale for functional assessment of USN (Azouvi et al., 2003; Ten Brink et al., 2013). It assesses performance in personal (body parts and body surface), peripersonal, and extrapersonal space, as well as in perceptual, representational, and motor domains. Nurses rated the severity of USN resulting in a range of 0 (no USN) to 30 (severe USN). The CBS total score was used as an outcome measure for the severity of the deficit in lateralized attention.

Other cognitive measures

The Mini-Mental State Examination (MMSE) is a cognitive screening instrument (Folstein, Folstein, & McHugh, 1975). It is an 11-point questionnaire assessing orientation, memory, attention, calculation, language, and constructive functions. The score ranges from 0 to 30; a score of less than 24 is regarded to reflect cognitive impairment.

The Stichting Afasie Nederland (SAN) task is a screening instrument for communication deficits, which focuses on verbal and auditory language and is filled out by the rehabilitation physician (Deelman, Koning-Haanstra, Liebrand, & van den Burg, 1981).

The score ranges from 1 (no communication possible via language) to 7 (normal speech and understanding of language).

The measure best *r* was derived from the object cancellation task, and depicts whether one searched in the same direction throughout the whole task, for example in a columnar fashion or row after row. To derive best *r*, we computed the Pearson correlation coefficient (*r*) from the linear regression of the x-values and y-values of all marked locations relative to the order in which they were marked. The highest absolute correlation of these two (best *r*) represents the degree to which calculations were pursued orthogonally (Mark, Woods, Ball, Roth, & Mennemeier, 2004). The best *r* value can range from 0 to 1, in which a higher value depicts a more efficient search.

The measure intersections rate indicates the amount of crossings with paths between previously cancelled targets. It has been shown that few intersections occur during efficient search (Woods & Mark, 2007). Further, the intersections rate differentiates between groups of stroke patients (Ten Brink, Van der Stigchel, Visser-Meily, & Nijboer, 2016). To compute the intersections rate, the total amount of path intersections was divided by the amount of cancellations that were not immediate revisits (Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2014). Thus, a high intersections rate indicates less organized search. Both best *r* and the intersections rate were computed using CancellationToolbox (Dalmaijer et al., 2014). Only data from the object cancellation task in extrapersonal space were used to compute best *r* and the intersections rate, because clicks in the peripersonal task were located too close to each other to reliably compute these measures.

Physical functioning and physical independence

The Motricity Index (Collin & Wade, 1990) assesses the severity of motor impairment after stroke. There are three items for the arm (pinch grip, elbow flexion, and shoulder abduction) as well as three for the leg (ankle dorsiflexion, knee extension, and hip flexion). Scores range from 0 (very severe motor impairment) to 100 (full motor function) per extremity (arm and leg).

Since a negative relation has been reported between USN and postural balance (Nijboer, Ten Brink, Van der Stoep, & Visser-Meily, 2014; van Nes et al., 2009), and disturbances in balance are related to problems in daily life functioning (Suzuki, Ohyama, Yamada, & Kanamori, 2002), the measure of postural balance was included in the current study. During the balance task, the average sitting position and postural sway of the patient were measured in two conditions: with eyes open and with eyes closed (Nijboer, Olthoff, Van der Stigchel, & Visser-Meily, 2014). The patient sat with their hands in their lap, on a Nintendo Wii Balance Board placed on a stool in front of a white wall. For each condition (eyes open and closed), four outcomes were taken into analysis. First, the centre of pressure (CoP) reflects the average sitting position on the Wii Balance Board. The mediolateral CoP represents the 'side-to-side position' (horizontal axis), and the anteroposterior CoP represents the 'front-to-back position' (vertical axis). To compare the left and right USN groups, both the relative as the absolute values of the average mediolateral CoP were used, to evaluate both the direction and the degree of deviation, respectively.

Shifts in CoP from the ideal weight distribution (i.e., a 50-50% weight distribution between the left and right and the front and back sensors) were seen as a measure of postural sway, or the ability to maintain balance (i.e., a large shift indicates poor balance). Mediolateral and anteroposterior postural sway (i.e., the mean variance of displacement) were calculated. The Wii Balance Board has shown good test-retest reliability of CoP path length and between devices, in validity and reliability comparisons with a force plate by Clark et al. (2010).

The Barthel Index (Collin, Wade, Davies, & Horne, 1988) assesses the level of independent functioning in ADL. Scores range from 0 (completely dependent) up to 20 (completely independent).

The Utrecht Scale for Evaluation of Rehabilitation (USER) covers physical independence (mobility and self-care; Post, van de Port, Kap, & Berdenis van Berlekom, 2009). The USER mobility subscale consists of 7 items including sitting, standing, transfers, and several forms of mobility, whereas the self-care subscale consists of 7 items including basic ADL. Total scores of each subscale range from 0 to 35, with higher scores reflecting better performance. The USER has been proven reliable, valid, and responsive (Post et al., 2009). Compared with the Barthel Index, the USER is more sensitive for improvement in patients with relatively good recovery, which can be attributed to the extended response categories used (Post et al., 2009). However, since the Barthel Index is more widely known, we additionally derived Barthel Index scores from the USER.

Lesion characteristics

The following lesion characteristics were retrieved from the medical charts: lesion side (left, right, or bilateral) and lesion focality (focal, diffuse, or bilateral).

For a subset of 81 ischaemic stroke patients, CT or MRI scans were available for lesion segmentation. Infarcts were manually segmented on transversal slices of either follow-up CT scans, or on T2 FLAIR sequences of MRI scans by a trained rater (JMB) who was blinded to clinical data. Infarct segmentations were transformed to the Montreal Neurological Institute (MNI)-152 template (Fonov, Evans, McKinstry, Almli, & Collins, 2009; Klein, Staring, Murphy, Viergever, & Pluim, 2010; Kuijf, Biesbroek, Viergever, Biessels, & Vincken, 2013), with an intermediate registration step using an age-specific CT and MRI template (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012), that served to improve the quality of the registrations. A more detailed description of the procedures for lesion segmentation and registration are provided elsewhere (Biesbroek et al., 2016; Biesbroek, van Zandvoort, Kappelle, et al., 2014). Quality checks of the registration results were performed by comparing the native scan to the lesion map in MNI space. For 45 patients, the coregistered lesion maps were manually adjusted to correct for slight registration errors using MRIcron (http://www.mccauslandcenter.sc.edu/crnl/mricron) by JMB.

To determine which brain regions were most strongly related to left and right USN, we performed a qualitative lesion overlay and subtraction analysis. In this analysis, lesion overlay and subtraction plots were generated for patients with left USN versus no USN, and right USN versus no USN, using MRIcron. The registered lesion maps were additionally used to compute normalized lesion volumes for these patients (Rorden, Karnath, & Bonilha, 2007).

Thus, the variables lesion side and lesion focality were retrieved from the medical charts for all patients, whereas lesion subtraction analyses and computation of lesion volumes were performed for a subset of 81 patients with lesion segmentations.

Data pre-processing and analysis

Since group sizes were unequal, and data were not normally distributed, differences between left, right, and no USN groups were tested with a Mann-Whitney test. Dichotomized variables were analysed with a Chi-Square test. In case of 5 expected count in less than 80% of cells, or a cell with zero expected count, the Fisher exact test was used.

For the Mann-Whitney test, effect sizes were calculated (with the formula: $r = z / \sqrt{(n)}$). For the Chi-Square test, phi (with a data table of 2 x 2) or Cramer's V (with a data table of >2 x 2) was calculated (with the formula: φ or $V = \sqrt{(\chi^2 / n(k - 1))}$). Effect sizes of .1, .3, and .5 were interpreted as small, medium, and large, respectively.

To answer our main question regarding differences between patients with left and right USN, all outcome measures were compared between patients with left and right USN in separate Mann-Whitney tests with a level of significance of $p = .05$.

Performance of patients with left and right USN was compared with performance of patients with no USN, to evaluate whether patients with USN differed from patients without USN. We used a Mann-Whitney test with a Bonferroni correction to avoid a family-wise error rate (adjusted level of significance $p = .025$).

Results

Inclusion

A flowchart of the included patients for this study is depicted in Figure 2.1. Of the 426 stroke patients admitted to the rehabilitation centre, 335 patients were included in behavioural analyses. Of these patients, 251 were classified as no USN, 53 as left USN, and 31 as right USN.[1] Left USN was more frequent than right USN (see Table 2.1 for statistics). In Table 2.1 the occurrence of region-specific USN is depicted for patients with left and right USN. These frequencies differed significant between patients with left and right USN. Left USN patients had USN in both regions of space more often compared to right USN patients (see Table 2.1 for statistics).

[1] Patients with left-sided USN omitted on average 6.34 targets on the left (*SD* = 6.31) and 1.27 targets on the right (*SD* = 1.75); patients with right-sided USN omitted on average 0.27 targets on the left (*SD* = 0.63) and 2.48 targets on the right (*SD* = 2.52).

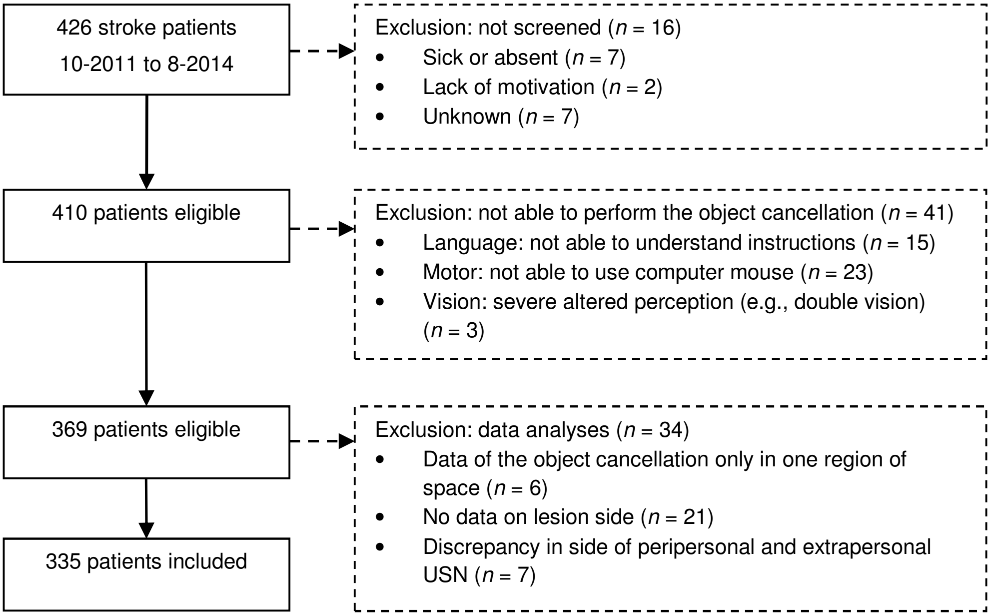


Figure 2.1 Flowchart of patient inclusion.

Table 2.1 Amount of patients per group

	Left USN	Right USN	Left vs. right USN
Group size	53	31	$\chi^2(1, n = 2) = 5.76$, $p = .016$*
Region of space, %			$\chi^2(2, n = 84) = 15.80$, $p < .001$*[1], $V = .43$
- Peripersonal	32.1	51.6	
- Extrapersonal	9.4	32.3	
- Both	58.5	16.1	

Abbreviation: USN, unilateral spatial neglect.

[1]Post-hoc comparisons showed that only the group size of the ‘Both’ group differed significantly between left and right USN patients.

*Statistically significant with alpha = .05

Demographic and stroke characteristics

Distributions of demographic and stroke characteristics are listed in Table 2.2. No differences in age, sex, handedness, stroke history, and aetiology were found between patients with left and right USN, left and no USN, or right and no USN. No difference was seen in time post-stroke onset at the moment of the USN screening between patients with left and right USN. Patients with left USN were screened at a later time post-stroke onset (5 days) than patients without USN.

Table 2.2 Demographic and stroke characteristics[1]

Outcome	Left USN	Right USN	No USN	Left vs. right USN	Left vs. no USN	Right vs. no USN
Age in years, median (IQR)	62 (16)	57 (18)	61 (16)	$U = 744.5$, $z = -0.71$, $p = .475$, $r = -.08$	$U = 6382.5$, $z = -0.46$, $p = .643$, $r = -.03$	$U = 3620$, $z = -0.63$, $p = .528$, $r = -.04$
Sex, % male	60.4	61.3	63.3	$X^2(1, n = 84) = .01$, $p = .934$, $\varphi = .01$	$X^2(1, n = 304) = .17$, $p = .684$, $\varphi = .02$	$X^2(1, n = 282) = .05$, $p = .823$, $\varphi = .01$
Handedness, %				$p = 1.00$	$p = .776$	$p = 1.00$
- Left	12.5	9.7	10.2			
- Right	87.5	90.3	88.5			
- Ambidexter	0	0	1.2			
Time post-stroke onset in days, median (IQR)	28 (22)	33 (28)	23 (15)	$U = 788.5$, $z = -0.31$, $p = .760$, $r = -.03$	$U = 4981$, $z = -2.80$, $p = .005$*, $r = -.16$	$U = 2932$, $z = -2.18$, $p = .029$, $r = -.13$
Stroke history, % first	89.1	88.9	90.9	$p = 1.00$	$p = .780$	$p = .726$
Aetiology, % ischaemic	79.5	82.1	82.0	$X^2(1, n = 72) = .07$, $p = .786$, $\varphi = .03$	$X^2(1, n = 250) = .15$, $p = .698$, $\varphi = .02$	$X^2(1, n = 234) = .00$, $p = .989$, $\varphi = .00$

Abbreviations: USN, unilateral spatial neglect.

[1]Ranges of group size: left USN = 44-53, right USN = 27-31, no USN = 206-251.

*Statistically significant with alpha = .05 (a Bonferroni correction was used for comparisons with the no USN group, alpha = .025).

Outcome measures

Severity of the lateralized attentional deficit

In Table 2.3 the results of the measures of lateralized attention are presented. A larger deficit in lateralized attention (absolute CoC-x) was found for patients with left than with right USN, in both peripersonal and extrapersonal space.

Regarding the line bisection, a deviation to the right was seen in patients with left USN compared to patients without USN, in both peripersonal and extrapersonal space. The deviation in patients with right USN did not differ from that in patients without USN, in neither peripersonal nor extrapersonal space. The magnitude of the deviation was larger for patients with left USN than for those with right USN in peripersonal and extrapersonal space, indicating a larger deficit in lateralized attention.

With respect to observations of USN in daily life, no discrepancies were found between patients with left and right USN, and between patients with right and no USN. Higher scores on the CBS were found, however, for patients with left USN than for patients without USN, indicating a deficit in lateralized attention in daily-life activities.

Table 2.3 Severity of the lateralized attentional deficit, median and IQR per outcome measure

Outcome	Left USN	Right USN	No USN	Left vs. right USN	Left vs. no USN	Right vs. no USN
Peripersonal space[1]						
OC CoC-x	.054 (.13)	.020 (.03)	0 (0)	U = 408, z = –3.84, p < .001*, r = –.42		
LB deviation	.09 (1.08)	–.26 (.40)	–.19 (.51)	U = 498, z = –2.72, p = .007*, r = –.30	U = 4434, z = –3.51, p < .001*, r = –.20	U = 3351, z = –0.85, p = .393, r = –.05
LB absolute deviation	.74 (.68)	.45 (.35)	.34 (.35)	U = 548.5, z = –2.23, p = .026*, r = –.25	U = 3795, z = –4.64, p < .001*, r = –.27	U = 3221, z = –1.17, p = .243, r = –.07
Extrapersonal space[1]						
OC CoC-x	.037 (.07)	.013 (.03)	0 (0)	U = 490.5, z = –3.08, p = .002*, r = –.34		
LB deviation	.27 (1.74)	–.23 (.68)	–.22 (.55)	U = 413, z = –3.62, p < .001*, r = –.40	U = 3921, z = –4.46, p < .001*, r = –.26	U = 3163.5, z = –1.18, p = .238, r = –.07
LB absolute deviation	.81 (1.09)	.51 (.52)	.42 (.37)	U = 481.5, z = –2.97, p = .003*, r = –.33	U = 3176, z = –5.78, p < .001*, r = –.34	U = 3086.5, z = –1.37, p = .171, r = –.08
Both distances[2]						
CBS	8.0 (15.9)	3.2 (7.1)	1.1 (4.0)	U = 141.5, z = –1.45, p = .146, r = –.22	U = 1332.5, z = –4.34, p < .001*, r = –.32	U = 674.5, z = –1.57, p = .117, r = –.12

Abbreviations: CBS, Catherine Bergego Scale; CoC, center of cancellation; IQR, Inter Quartile Range; LB, line bisection; OC, object cancellation; USN, unilateral spatial neglect.

[1]Group size ranges: left USN = 52-53, right USN = 30-31, no USN = 243-251. [2]Group sizes: left USN = 33, right USN = 12, no USN = 153.

*Statistically significant with alpha = .05 (a Bonferroni correction was used for comparisons with the no USN group, alpha = .025).

Other cognitive measures

Boxplots with scores on all four cognitive measures are depicted in Figure 2.2. Patients with left USN showed comparable general cognitive functioning (MMSE) to that of patients with right or no USN. Patients with right USN showed a lower cognitive functioning (2 points lower on the MMSE) than patients without USN (Table 2.4).

No difference was seen between patients with left and right USN, left and no USN, and right and no USN regarding communication impairments as measured with the SAN.

Regarding search consistency at the object cancellation task, no differences were seen between patients with left and right USN, left and no USN, and right and no USN. Search organization differed between patients with left and right USN, and left and no USN, with higher intersections rates for patients with left USN, indicating less organized search. No differences were seen between patients with right and no USN.

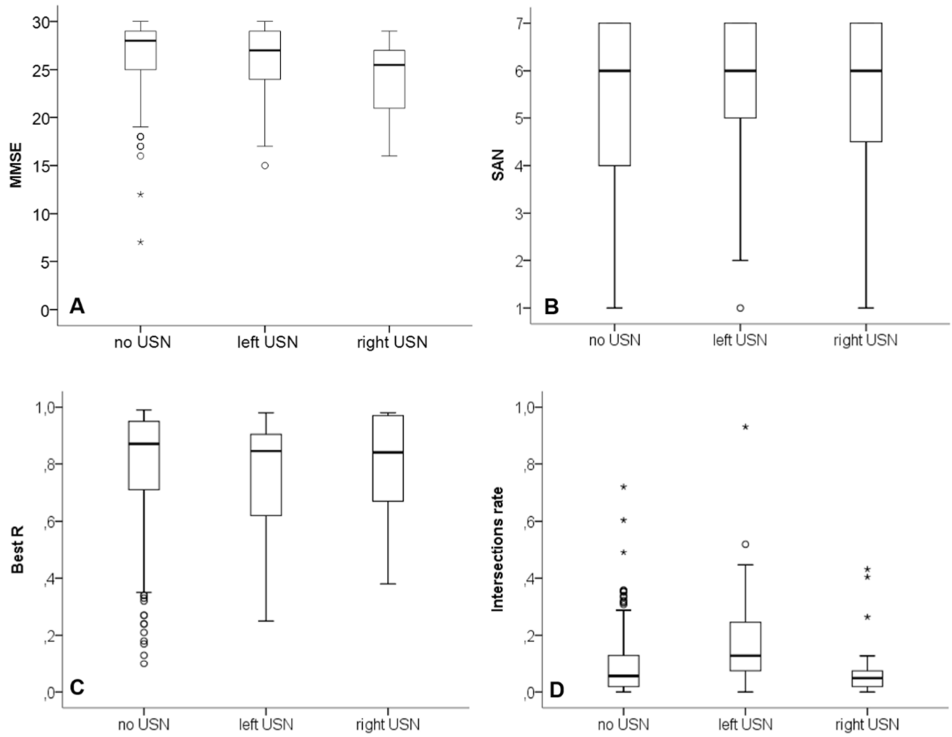


Figure 2.2 Boxplots of the (a) Mini-Mental State Examination (MMSE), (b) Stichting Afasie Nederland (SAN), (c) best *R*, and (d) intersections rate scores for the no, left, and right unilateral spatial neglect (USN) groups.

Table 2.4 Other cognitive measures, median and IQR per measure[1]

Outcome	Left USN	Right USN	No USN	Left vs. right USN	Left vs. no USN	Right vs. no USN
MMSE	27 (5)	26 (6)	28 (4)	U = 249, z = −1.52, p = .129, r = −.20	U = 2651, z = −1.36, p = .173, r = −.10	U = 940.5, z = −2.63, p = .009*, r = −.19
SAN	6 (2)	6 (3)	6 (3)	U = 466, z = −0.52, p = .600, r = −.06	U = 4234, z = −0.12, p = .901, r = −.01	U = 2295.5, z = −0.52, p = .604, r = −.03
OC best R	.85 (.29)	.84 (.30)	.87 (.24)	U = 686, z = −0.91, p = .364, r = −.10	U = 5673.5, z = −1.24, p = .215, r = −.07	U = 3527, z = −0.36, p = .719, r = −.02
OC intersections rate	0.13 (0.17)	0.05 (0.06)	0.06 (0.11)	U = 391.5, z = −3.74, p < .001*, r = −.41	U = 3572.5, z = −4.99, p < .001*, r = −.29	U = 3466.5, z = −0.51, p = .611, r = −.03

Abbreviations: IQR, Inter Quartile Range; MMSE, Mini-Mental State Examination; OC, object cancellation; SAN, Stichting Afasie Nederland; USN, unilateral spatial neglect.

[1]Group size ranges: left USN = 37-53, right USN = 18-30, no USN = 167-245.

*Statistically significant with alpha = .05 (a Bonferroni correction was used for comparisons with the no USN group, alpha = .025).

Physical functioning and physical independence

Table 2.5 shows the outcomes of the physical functioning and physical independence domain. With respect to motor strength (Motricity Index arm and leg), no differences were obtained between patients with left, right, and no USN.

Data of two patients (2.8%) were considered outliers in multiple balance outcomes and were excluded from all balance analyses; both patients were part of the left USN group. Patients with right USN were shifted more to one side of the balance board (either the left or right, as measured with the absolute CoP mediolateral deviation) than patients with left USN, only with eyes closed (see Figure 2.3). Neither the relative CoP mediolateral and anteroposterior deviation (i.e., the average deviation) nor the postural sway differed between patients with left and right USN. Patients without USN did not differ from patients with left and right USN on any of the balance measures.

Physical independence at admission, as measured with the Barthel Index, did not differ between patients with left, right, and no USN. Physical independence (Barthel Index) in the first week did not differ between patients with left and right USN. Compared to patients without USN, physical independence in the first week was lower for patients with right and left USN. At discharge, no difference was seen regarding physical independence between patients with left and right USN. Patients with left and right USN had lower physical independence scores than patients without USN.

In the first week, mobility (as measured with the USER) did not differ between patients with left and right USN. However, it was worse for patients with right and left USN than for patients without USN (see Figure 2.4). At discharge, no differences were seen regarding mobility between patients with left, right, and no USN.

Regarding self-care (as measured with the USER) in the first week, patients with left USN did not differ from patients with right and no USN. However, self-care was worse for patients with right and left USN compared to patients without USN. At discharge, patients with left USN had worse self-care than patients without USN at discharge; this was a trend for patients with right USN.

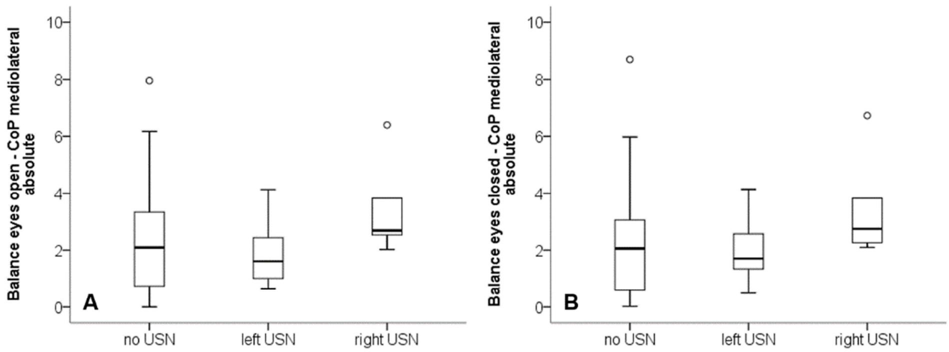


Figure 2.3 Boxplots with the absolute balance centre of pressure (CoP) mediolateral value for (a) eyes open and (b) eyes closed, for the no, left, and right unilateral spatial neglect (USN) groups.

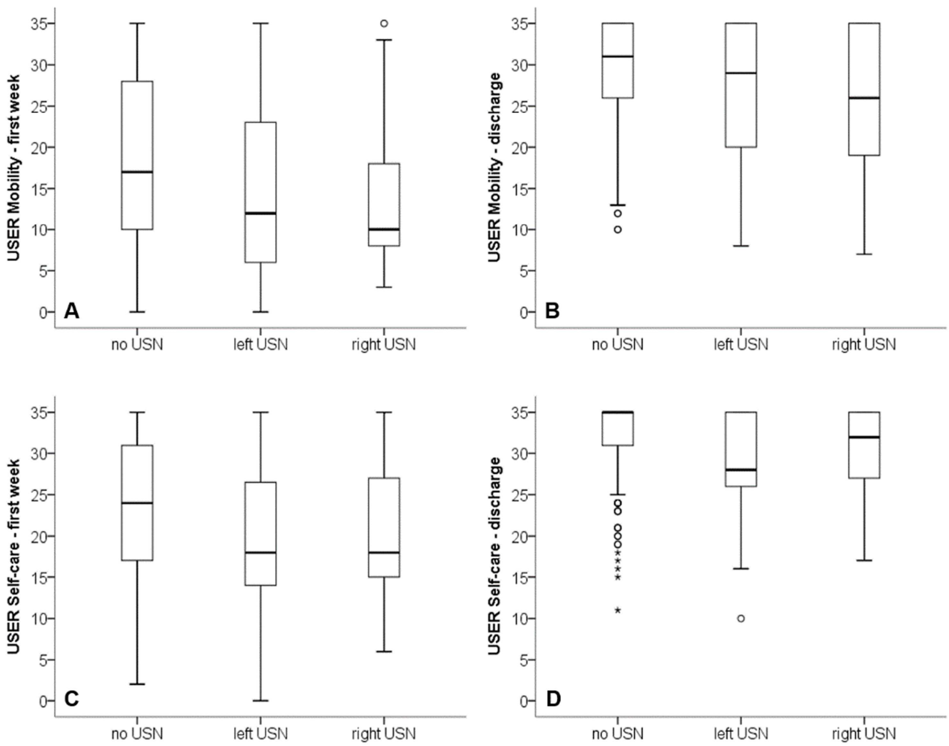


Figure 2.4 Boxplots of the Utrecht Scale for Evaluation of Rehabilitation (USER) mobility scale (a) in the first week and (b) at discharge, and boxplots of the USER self-Care (c) in the first week and (d) at discharge, for the no, left, and right USN groups.

Table 2.5 **Physical functioning and physical independence, median and IQR per measure**

Outcome	Left USN	Right USN	No USN	Left vs. right USN	Left vs. no USN	Right vs. no USN
Motricity Index arm[1]	72 (100)	76 (75)	76 (61)	$U = 381.5$, $z = -1.00$, $p = .319$, $r = -.13$	$U = 3058$, $z = -1.81$, $p = .071$, $r = -.12$	$U = 2154$, $z = -0.16$, $p = .876$, $r = -.01$
Motricity Index leg[1]	75 (86)	83 (45)	91 (50)	$U = 351.5$, $z = -1.44$, $p = .151$, $r = -.18$	$U = 2908.5$, $z = -2.13$, $p = .033$, $r = -.14$	$U = 2146.5$, $z = -0.10$, $p = .920$, $r = -.01$
Barthel Index - admission[1]	11 (10)	11 (7)	14 (9)	$U = 482$, $z = -0.32$, $p = .751$, $r = -.04$	$U = 3388$, $z = -1.78$, $p = .075$, $r = -.12$	$U = 1682.5$, $z = -1.67$, $p = .094$, $r = -.12$
Barthel Index - first week[1]	13 (9)	12 (8)	17 (8)	$U = 662.5$, $z = -0.35$, $p = .724$, $r = -.04$	$U = 3966$, $z = -2.58$, $p = .010^*$, $r = -.16$	$U = 2140.5$, $z = -2.80$, $p = .005^*$, $r = -.18$
Barthel Index - discharge[1]	20 (2)	20 (2)	20 (0)	$U = 550$, $z = -0.18$, $p = .859$, $r = -.02$	$U = 3864.5$, $z = -2.81$, $p = .005^*$, $r = -.18$	$U = 2041$, $z = -2.69$, $p = .007^*$, $r = -.17$
USER mobility - first week[1]	12 (19)	10 (11)	17 (18)	$U = 693$, $z = -0.18$, $p = .856$, $r = -.02$	$U = 4163$, $z = -2.29$, $p = .022^*$, $r = -.14$	$U = 2235$, $z = -2.48$, $p = .013^*$, $r = -.16$
USER mobility - discharge[1]	29 (16)	26 (16)	31 (9)	$U = 551$, $z = -0.14$, $p = .886$, $r = -.02$	$U = 3869.5$, $z = -1.81$, $p = .071$, $r = -.11$	$U = 2045.5$, $z = -1.74$, $p = .082$, $r = -.11$
USER self-care - first week[1]	18 (13)	18 (12)	24 (14)	$U = 681.5$, $z = -0.15$, $p = .879$, $r = -.02$	$U = 3906$, $z = -2.72$, $p = .007^*$, $r = -.17$	$U = 2315.5$, $z = -2.32$, $p = .021^*$, $r = -.15$
USER self-care - discharge[1]	28 (9)	32 (9)	35 (4)	$U = 506.5$, $z = -0.70$, $p = .485$, $r = -.08$	$U = 3269.5$, $z = -3.65$, $p < .001^*$, $r = -.23$	$U = 2028$, $z = -2.17$, $p = .030$, $r = -.14$
Balance eyes open[2]						
CoP anteroposterior	–0.64 (2.05)	0.37 (4.58)	0.37 (1.64)	$U = 25$, $z = -1.23$, $p = .219$, $r = -.28$	$U = 231$, $z = -1.60$, $p = .110$, $r = -.20$	$U = 142$, $z = -0.21$, $p = .832$, $r = -.03$
CoP mediolateral	0.64 (3.55)	–2.62 (6.66)	0.10 (3.88)	$U = 22$, $z = -1.49$, $p = .136$, $r = -.34$	$U = 321$, $z = -0.07$, $p = .946$, $r = -.01$	$U = 93$, $z = -1.51$, $p = .131$, $r = -.20$

CoP mediolateral	1.61	2.69	2.09	*U* = 17, *z* = –1.93,	*U* = 308, *z* = –0.29,	*U* = 96, *z* = –1.43,
absolute	(1.93)	(2.06)	(2.63)	*p* = .054, *r* = –.44	*p* = .773, *r* = –.04	*p* = .153, *r* = –.19
Sway	0.009	0.002	0.005	*U* = 22, *z* = –1.49,	*U* = 259, *z* = –1.12,	*U* = 93, *z* = –1.51,
anteroposterior	(0.009)	(0.010)	(0.011)	*p* = .136, *r* = –.34	*p* = .262, *r* = –.14	*p* = .131, *r* = –.20
Sway mediolateral	0.009	0.002	0.006	*U* = 20, *z* = –1.67,	*U* = 213, *z* = –1.90,	*U* = 117, *z* = –0.87,
	(0.028)	(0.021)	(0.009)	*p* = .096, *r* = –.38	*p* = .057, *r* = –.24	*p* = .382, *r* = –.12
Balance eyes closed[2]						
CoP	–0.21	0.41	0.41	*U* = 29, *z* = –0.88,	*U* = 251, *z* = –1.26,	*U* = 134, *z* = –0.42,
anteroposterior	(1.94)	(4.40)	(1.73)	*p* = .380, *r* = –.20	*p* = .209, *r* = –.16	*p* = .672, *r* = –.06
CoP mediolateral	0.49	–2.75	–0.03	*U* = 24, *z* = –1.32,	*U* = 323, *z* = –0.03,	*U* = 96, *z* = –1.43,
	(3.44)	(6.69)	(3.90)	*p* = .188, *r* = –.30	*p* = .973, *r* = .00	*p* = .153, *r* = –.19
CoP mediolateral	1.71	2.75	2.06	*U* = 15, *z* = –2.11,	*U* = 318, *z* = –0.12,	*U* = 94, *z* = –1.48,
absolute	(1.62)	(2.33)	(2.57)	*p* = .035*, *r* = –.48	*p* = .905, *r* = –.01	*p* = .138, *r* = –.20
Sway	0.006	0.005	0.005	*U* = 28, *z* = –0.97,	*U* = 248, *z* = –1.31,	*U* = 132, *z* = –0.48,
anteroposterior	(0.011)	(0.011)	(0.006)	*p* = .335, *r* = –.22	*p* = .191, *r* = –.16	*p* = .633, *r* = –.06
Sway mediolateral	0.006	0.005	0.006	*U* = 30, *z* = –0.79,	*U* = 294, *z* = –0.53,	*U* = 127, *z* = –0.61,
	(0.010)	(0.015)	(0.013)	*p* = .430, *r* = –.18	*p* = .599, *r* = –.07	*p* = .542, *r* = –.08

Abbreviations: CoP, Center of Pressure; IQR, Inter Quartile Range; USER, Utrecht Scale for Evaluation of Rehabilitation; USN, unilateral spatial neglect.

[1]Group size ranges: left USN = 39-49, right USN = 23-29, no USN = 186-217. [2]Group sizes: left USN = 13, right USN = 6, no USN = 50.

*Statistically significant with alpha = .05 (a Bonferroni correction was used for comparisons with the no USN group, alpha = .025).

Lesion characteristics

The side of the lesion differed significantly between patients with left and right USN and between patients with left and no USN (Table 2.6), with more right-hemisphere damage in patients with left USN (77.4%) than in those with right (35.5%), and no USN (47.4%). No difference was seen between patients with right and no USN regarding lesion side. Note that 17% to 35.5% of patients showed ipsilesional USN. Lesion focality did not differ between patients with left, right, and no USN.

Figures 2.5A-C show the overlay plots of patients with no USN (n = 53), left USN (n = 19), and right USN (n = 9), and Figures 2.5D-E show the qualitative lesion subtraction plots of patients with and without USN. Left USN was predominantly associated with lesions in the postcentral gyrus, supramarginal gyrus, angular gyrus, parietal operculum cortex, central operculum cortex, insula, Heschl's gyrus, and frontal operculum cortex of the right cerebral hemisphere. In contrast, regions that were more frequently lesioned in patients with right USN were not clearly lateralized and included left- and right-hemispheric temporo-parietal regions. Lesion volume did not differ between patients with left and right USN. Patients with left USN had significantly higher lesion volume than patients with no USN, whereas patients with right and no USN did not differ regarding lesion volume.

Table 2.6 Lesion characteristics

Outcome	Left USN	Right USN	No USN	Left vs. right USN	Left vs. no USN	Right vs. no USN
Retrieved from medical chart[1]						
Lesion side, %				$p < .001$*	$X^2(2, n = 304) = 16.90$, $p < .001$*, $V = .24$	$X^2(2, n = 282) = 2.30$, $p = .317$, $V = .09$
- Left	17.0	61.3	47.0			
- Right	77.4	35.5	47.4			
- Bilateral	5.7	3.2	5.6			
Lesion focality, %				$p = .799$	$p = .269$	$p = .092$
- Focal	75.6	70.0	85.1			
- Diffuse	17.1	25.0	9.4			
- Bilateral	7.3	5.0	5.5			
Retrieved from CT or MRI scan[2]						
Lesion volume in ml, median (IQR)	95 (218)	85 (182)	30 (82)	$U = 63$, $z = -1.11$, $p = .268$, $r = .21$	$U = 239$, $z = -3.38$, $p = .001$*, $r = -.40$	$U = 190$, $z = -0.97$, $p = .332$, $r = -.12$

Abbreviations: USN, unilateral spatial neglect.

[1]Group size ranges: left USN = 41-53, right USN = 20-31, no USN = 181-251. [2]Group sizes: left USN = 19, right USN = 9, no USN = 53.

*Statistically significant with alpha = .05 (a Bonferroni correction was used for comparisons with the no USN group, alpha = .025).

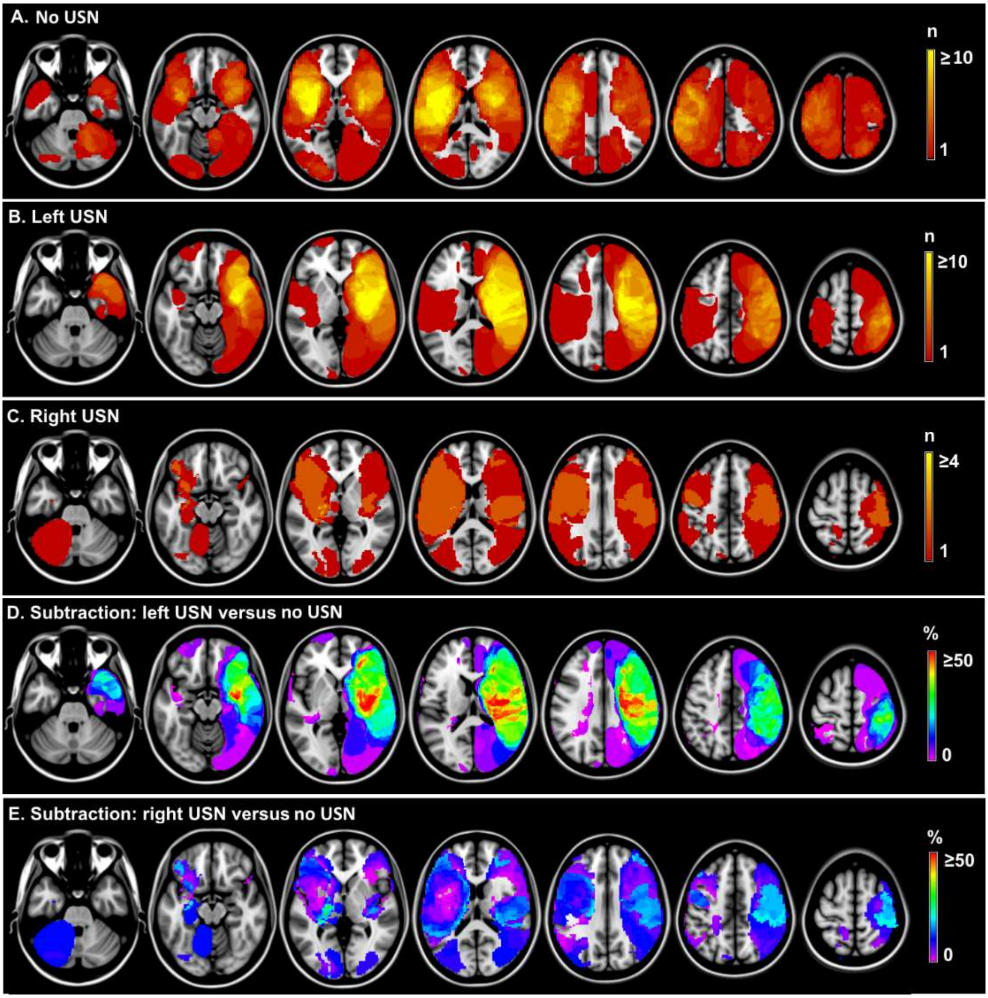


Figure 2.5 Lesion overlay plots and subtraction plots. Damaged voxels are depicted for patients with (A) no unilateral spatial neglect (USN; *n* = 53), (B) left USN (*n* = 19), and (C) right USN (*n* = 9). The colored bar indicates the number of patients with a lesion for each voxel. The final two panels show subtraction plots of no USN patients versus patients with (D) left USN, and (E) right USN. Voxels in the lesion subtraction plot that are more often damaged in the USN group versus the no USN group are shown on a scale ranging from pink (1% absolute difference in lesion frequency) to red (>50% absolute difference). Results are projected on the MNI 1-mm template (*z* coordinates: −30, −15, 0, 15, 30, 45, 60). The right hemisphere is depicted on the right.

Discussion

In this study, data was collected in cognitive and physical domains for a large cohort of stroke patients. The primary aim was to investigate distinctions and similarities between patients with left and right USN regarding frequency, severity, region specificity (i.e., peripersonal, extrapersonal), general cognition, physical functioning, and physical independence. The secondary aim was to compare lesion characteristics between patients with left versus right USN. This study is one of the first to provide an extensive overview of different outcomes in multiple domains.

To be able to adequately pinpoint and thus interpret the current results and its impact, it is important to note that the sample of stroke patients were admitted to inpatient rehabilitation, in the subacute phase post-stroke onset. In the Netherlands, this patient population is general relatively young and moderately impaired. As a direct result, the current results might not generalize to an older and/or more severely impaired population. However, the current results are still of major importance for diagnostics and treatment in the subacute phase post-stroke, as treatment in this phase is most intensive.

Frequency, severity, and region-specific unilateral spatial neglect

Overall, left, right, and no USN patients were comparable regarding age, sex, handedness, time post-stroke onset, stroke aetiology, and stroke history. Of the total sample of 335 patients, 86 patients showed USN. Of the USN patients, 63.1% showed left-sided and 36.9% showed right-sided USN. This ratio is in line with other studies who included patients in the subacute phase after stroke: left USN is more frequent than right USN after 3 months post-stroke onset (Stone et al., 1991; Wee & Hopman, 2008). Overall percentages of USN (15.8% left USN and 9.3% right USN) were somewhat lower compared to other studies (Ringman et al., 2004; Stone, Halligan, & Greenwood, 1993; Wee & Hopman, 2008). This might be the result of the number of tests that were used to assess USN.

Although USN is commonly known as a contralesional symptom, the current results confirm previous studies that ipsilateral neglect also exists (Kim et al., 1999; Kwon & Heilman, 1991), with a prevalence of 17% to 35.5% for left and right USN, respectively. While previous studies have detected ipsilateral neglect with the line bisection task, the current study shows that the object cancellation task is also sensitive to detect this symptom. It has been hypothesized that ipsilateral USN particularly results from fronto-subcortical brain damage (Kim et al., 1999).

With respect to the severity of the lateralized attentional deficit, as measured with the shape cancellation and line bisection task, the magnitude of lateralized inattention was larger in patients with left USN (i.e., more omissions, a larger asymmetry of omissions, and a larger deviation on the line bisection) than in patients with right USN. Contrary, left and right USN had a comparable negative impact on behaviour of USN (i.e., comparable scores on the CBS). When compared to patients without USN, left USN - but not right USN - appeared to have a larger negative impact on behaviour of USN in ADL.

Last, with respect to region specificity, left peripersonal and extrapersonal USN occurred as frequently as right peripersonal and extrapersonal USN. However, USN for both peripersonal and extrapersonal regions of space was more frequent in patients with left than in those with right USN. This could relate to the specific brain areas that were damaged. Possibly, lesions were larger in patients with left USN, resulting in both peripersonal and extrapersonal USN, and a larger deficit in lateralized attention. Several overlapping brain structures (i.e., the middle temporal and frontal cortex as well as the anterior cingulate cortex) are possibly involved in both peripersonal as extrapersonal USN (Aimola et al., 2012). In prior research, lesion size and the severity of the deficit in lateralized attention correlated (Leibovitch et al., 1998).

In the current study, 3.5% of patients (n = 15) were excluded due to problems with understanding task instructions. Excluding patients with (mild) difficulties in understanding task instructions might lead to under detection of especially right USN (i.e., left-hemisphere lesions; Bowen, McKenna, & Tallis, 1999; Suchan et al., 2012; Wee & Hopman, 2008). However, in several studies the assessment of USN was feasible in patients with aphasia (Chen, Chen, et al., 2015; Wee & Hopman, 2008), and those studies reported that the occurrence of left USN was still higher than that of right USN. In addition, Ringman et al. (2004) corrected for the possibility of a selection bias, by considering patients with left-hemisphere damage with severe aphasia as USN patients. Even with this strict correction, the differences between hemispheres with regard to incidence and severity remained in their study.

Cognitive measures

General cognitive status, as measured with the MMSE, was found to be marginally lower in patients with right USN than in those with no USN. One explanation might be that language is a key component in the MMSE. In our sample, patients with severe language deficits (especially understanding) were excluded from the neglect screening, yet left-hemisphere damage might also result in very subtle language deficits that are likely to picked up with the MMSE. Overall, MMSE scores were fairly high in our sample, and no difference was seen between patients with left and right USN, and left and no USN. Both findings are in line with those of another, comparable study (Nijboer, van de Port, et al., 2013).

Search efficiency was found to be poorer in patients with left USN than in those with right and no USN, which suggests that patients with left USN might have poorer visual overview or spatial working memory (see also Ten Brink, Van der Stigchel, et al., 2016). As the right hemisphere has been suggested to be dominant for visuospatial processing and representation (Pisella et al., 2011), spatial working memory problems (which are a subcomponent of USN) presumably result more often following right-hemisphere damage.

Physical functioning and physical independence

No differences in motor impairment of the arm and leg were found between patients with left, right, and no USN, which is in contrast with prior studies (Meyer et al., 2016; Nijboer, Kollen, et al., 2014). In, for example, the study by Nijboer et al. (2014), a hampering effect of USN on motor functioning and motor recovery was described. However, in the Nijboer et al. study (2014), only patients with motor impairment in the first week post-stroke onset were included, and recovery trajectories were calculated for the first year post-stroke. In the current study, only a very limited time-window was tested in a different class of patients (namely, patients relatively young and fit enough for inpatient rehabilitation), which might explain the apparent difference in impact of USN on motor impairment.

Patients with left and right USN did not differ from each other regarding Barthel Index at admission, nor mobility and self-care in the first week and at discharge. However, in the first week, patients with USN had lower mobility and self-care scores than patients without USN. At discharge, patients with left USN had lower self-care scores than patients without USN. This is in line with prior studies, showing that USN is negatively associated with performance in other domains (Wee & Hopman, 2008).

With respect to sitting balance with eyes closed, right USN patients showed a larger absolute deviation from left to right than left USN patients. This effect was not seen in the eyes-open situation. This implies that patients with left and right USN differ in other sensory modalities beside visual information, at least in the current sample. Figure 2.5 shows that right USN patients are proportionally more often subject to lesions in the cerebellum. As the cerebellum plays a major role in maintaining balance and posture, this may explain the difference found in the current study. There was no difference with respect to the direction of this deviation. Regarding the other balance outcomes, left and right USN patients showed comparable deviations from front to back, as well as comparable postural sway. Additionally, no differences were found between either USN group and the non-USN group. It should be noted that due to task demands (i.e., being able to sit unaided for 30 s), patients with severe balance problems were excluded.

Lesion characteristics

A lateralization of right-hemisphere damage in patients with left USN was seen (77.4% right brain damage). However, no clear lateralization regarding lesion location was seen in patients with right USN: only 61.3% of patients had left brain damage. Lesion focality did not differ between patients with left, right, and no USN.

Our lesion subtraction analyses demonstrated that left USN was associated with right-hemispheric temporo-parietal and frontal lesions, predominantly involving the postcentral gyrus, supramarginal gyrus, angular gyrus, parietal operculum cortex, central operculum cortex, insula, Heschl's gyrus, and frontal operculum cortex of the right cerebral hemisphere, which is in line with earlier findings (Danckert & Ferber, 2006; Karnath, Berger, Küker, & Rorden, 2004). In contrast, regions that were more frequently lesioned in patients with right USN were not clearly lateralized and included left- and right-hemispheric temporo-parietal regions. This is in line with prior research (Mesulam, 1981). Lesion volume did not differ between patients with left and right USN. For patients with left USN - but not for patients with right USN - lesion volume was larger than that for patients without USN. It is important to note that these results were based on a relatively small sample (9 right and 19 left USN patients); especially, potential differences in volumes between no USN and right USN could have been missed due to limited statistical power. The modest sample size precluded the option of voxel-based lesion symptom-mapping analyses. Nevertheless, these findings suggest that the differences found at the behavioural level (mainly severity of the lateralized attentional deficit and its consequences in basic ADL) are not a mere consequence of larger lesions or different focality for left versus right USN. In a prior study, comparable brain areas (e.g., posterior cortical lesions) were associated with both left and right USN (Beis et al., 2004), whereas in another study, right-hemisphere-damaged USN patients had mostly posterior lesions, and left-hemisphere-damaged USN patients had mostly anterior lesions (Ogden, 1985). Larger numbers of stroke patients are needed to fully unravel neuronal correlates of left and right USN.

Unilateral spatial neglect versus lateralized inattention

As already mentioned in the introduction, there is an ongoing debate about proper terminology for the neuropsychological disorder that is central in our paper: unilateral spatial neglect. For example, another term that is also used in science as well as clinical practice is visuospatial neglect, stressing the sensory modality, although the visual domain is by no means central to this disorder. In our view, neglect is a complex and heterogeneous *syndrome*. The core cognitive deficit, however, is *lateralized inattention*, yet non-lateralized cognitive deficits have also been associated with the neglect syndrome, such as impairments in arousal and more general awareness. In clinical practice, (the magnitude of) lateralized inattention is measured with a neuropsychological assessment, and patients who fail such tests are generally diagnosed with neglect. The same is true for many scientific studies. Consensus on better use of proper terminology for either the syndrome or the specific lateralized inattention would therefore not only enhance clarity on the specificity of impairments in patients (both in science and clinical practice), but also improve assessment and treatment of patients.

Limitations

The retrospective nature is a limitation of the current study. Data quality was dependent on the consistency of the individual nurses, physical therapists, and neuropsychologists. For some of the measures (e.g., balance) the group sizes were small, reducing statistical power. A limitation of the overlay and subtraction analyses is that it can only be applied to voxels that are damaged in a certain amount of patients. As a consequence, we cannot draw any conclusions regarding regions that were not affected in any of the patients. In the current study, no data on visual field deficits, such as hemianopia, were present, and effects of hemianopia on our outcome measures could not be evaluated. However, hemianopia would have affected both groups, as the disorder is not specifically related to one of the hemispheres. In addition, anosognosia (i.e., a deficit in self-awareness where the patient seems unaware of the existence of the deficit) and anosodiaphoria (i.e., acquired indifference to the presence of the deficit, specifically paralysis) are two disorders more commonly observed in patients with right-hemisphere lesions compared to left-hemisphere lesions (Pia, Neppi-Modona, Ricci, & Berti, 2004). Systematic screening for these disorders was not part of standard clinical care. It might be that patients with anosognosia and/or especially anosodiaphoria are less likely to be admitted to a rehabilitation centre for inpatient rehabilitation as a certain amount of motivation and endurance is mandatory for keeping up with the intense schedules and pace, resulting in a underrepresentation of USN patients with right-hemispheric damage. Due to the design of this study - a retrospective cohort study - and the lack of systematic information from the patient files with respect to these disorders, we cannot report frequencies of these disorders in our current samples.

The allocation of the patients in the three groups was based on a single test that was administered in two regions of space. No distinction was made between patients with USN in peripersonal, extrapersonal, or both regions of space. Furthermore, seven patients were excluded based on discrepant results between regions of space. Since consequences of peripersonal and extrapersonal USN on the level of activities differ (Nijboer, Ten Brink, Kouwenhoven, & Visser-Meily, 2014; Nijboer, Ten Brink, Van der Stoep, et al., 2014), it would have been of great value to separately analyse these groups. Unfortunately, we were unable to do so due to a lack of statistical power. To prevent under detection, one might consider using a test-battery and composed score of three (types of) tests: one traditional neglect-test (e.g., a cancellation task), one functional test such as the CBS (Azouvi et al., 1996), and one test that is insensitive to aphasia, like the Albert's Test (Suchan et al., 2012). For the current study, this was not feasible as not enough patients were tested with three tests for neglect. In addition, other types of USN, such as personal or motor neglect, were not thoroughly investigated as no specific measures were used to determine these types of neglect.

As mentioned above, the current study was performed in a distinct class of patients - namely, patients relatively young and fit enough for inpatient rehabilitation. Therefore, it remains to be seen whether differences between left and right USN patients exist in the acute and/or chronic phase post-stroke onset and whether differences in the timing of recovery of left versus right USN patients exist.

Conclusion

Left and right USN are both common after stroke. The current study shows that left USN is more frequent, and the deficit in lateralized attention is more severe with respect to the neuropsychological outcomes and observations of USN in ADL. Patients with right USN showed poorer overall cognition than those with no USN, whereas patients with left USN showed problems with search organization. Patients with right USN had poorer balance, while no differences were seen on other motor functions or physical independence in ADL. Left USN was associated with lesions in the right hemisphere predominantly involving temporo-parietal and frontal regions, whereas no clear lateralization was observed for right USN.

With respect to several aspects of cognition, physical functioning, and physical independence, left and right USN were associated with poorer performance than no USN. From a clinical perspective, it is good to systematically screen for USN, both after right- and after left-hemisphere damage.

Supplementary Table 2.1 Data collection

Measure	Moment	Who
Brain scans (MRI or CT) - Total infarct volume	Before admission to rehabilitation	Hospital
SAN MMSE Barthel Index Demographic characteristics - Age - Sex - Handedness Stroke characteristics - Date stroke - Stroke history - Aetiology Lesion characteristics - Lesion side - Lesion focality	Admission	Rehabilitation physician
USER	First week after admission and in the week of discharge	Nurse
CBS	Within two weeks after admission	Nurse
USN screening - Object cancellation - Line bisection - Balance	Within two weeks after admission	Neuropsychologist

Abbreviations: CBS, Catherine Bergego Scale; MMSE, Mini-Mental State Examination; SAN, Stichting Afasie Nederland; USER, Utrecht Scale for Evaluation of Rehabilitation; USN, unilateral spatial neglect.

Chapter 3

Peripersonal and extrapersonal visuospatial neglect based on cancellation versus bisection: A brain lesion-symptom mapping study

Ten Brink, A. F., Biesbroek, J. M., Oort, Q., Visser-Meily, J. M. A., Nijboer, T. C. W. (Under review). Peripersonal and extrapersonal visuospatial neglect based on cancellation versus bisection: A brain lesion-symptom mapping study.

Abstract

Introduction. Visuospatial neglect has been reported in peripersonal and extrapersonal space. Dorsal areas are hypothesized to be related with peripersonal, and ventral areas with extrapersonal neglect. We aimed to evaluate neural substrates of peripersonal and extrapersonal neglect, separately for cancellation and bisection tasks, as they assess different aspects of attention. *Methods*. This was a retrospective study, including stroke patients admitted for inpatient rehabilitation. Approximately 1 month post-stroke onset, computerized cancellation and bisection tasks were administered at 30 cm and 120 cm. We collected CT or MRI scans (made at admission to the hospital), and performed voxel-based lesion-symptom mapping with the centre of cancellation and the deviation on the line bisection, in peripersonal and extrapersonal space, as continuous outcome measures. *Results*. We included 98 patients for the shape cancellation and 129 for the line bisection analyses. Based on shape cancellation, the right parahippocampal gyrus, right hippocampus, and right thalamus were related to peripersonal neglect. These areas were also related to extrapersonal neglect, together with the superior parietal lobule, angular gyrus, supramarginal gyrus, lateral occipital cortex, planum temporale, and superior temporal gyrus (all within the right hemisphere). Based on line bisection, no regions were significantly related with peripersonal neglect. The thalamus, precuneous cortex, multiple structures in the occipital and temporal lobe and intracalcarine cortex (all right hemisphere) were associated with extrapersonal neglect. *Discussion.* Overlapping brain areas were related to peripersonal and extrapersonal neglect. Future studies should include sensitive, continuous measures of neglect, a large sample of unselected stroke patients, and focus on functional networks.

Introduction

Visuospatial neglect ("neglect") is a disabling disorder that is frequently observed after a stroke. It is a complex, multi-component disorder (Bisiach, Perani, Vallar, & Berti, 1986; Husain & Rorden, 2003), and can occur in most, if not all, sensory modalities as well as in the motor domain (Corbetta, 2014; Jacobs et al., 2012; Laplane & Degos, 1983). Patients with neglect have a deficit in lateralized attention (Heilman & Abell, 1980). They show no, or less, explorative behaviours and actions directed towards stimuli (usually) on the contralesional side. The lateralized attention deficit is more common and more severe after a stroke in the right hemisphere (Chen, Chen, et al., 2015; Gainotti et al., 1972; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017). Negative consequences in daily life activities, however, are largely comparable between left and right-sided neglect (Ten Brink, Verwer, et al., 2017). Neglect can manifest in peripersonal space (i.e., within reaching distance; near) or extrapersonal space (i.e., beyond reaching distance; far) (Aimola et al., 2012; Halligan, Fink, Marshall, & Vallar, 2003; Keller, Schindler, Kerkhoff, Rosen, & Golz, 2005; Van der Stoep et al., 2013). Traditional paper-and-pencil testing methods can, almost by definition, only assess neglect in peripersonal space. However, double dissociations and differences regarding neglect severity exist between peripersonal and extrapersonal neglect (Aimola et al., 2012; Cowey, Small, & Ellis, 1994, 1998; Keller et al., 2005; Pitzalis, Di Russo, Spinelli, & Zoccolotti, 2001; Van der Stoep et al., 2013). In addition, peripersonal and extrapersonal neglect differ regarding consequences on activities of daily living (Appelros, Nydevik, Karlsson, Thorwalls, & Seiger, 2003; Nijboer, Ten Brink, Kouwenhoven, et al., 2014; Nijboer, Ten Brink, Van der Stoep, et al., 2014).

The aim of the current study was to identify brain lesion locations associated with neglect in peripersonal and extrapersonal space. Previc (1998) was one of the first to argue that processing visuospatial information in different regions of space relies on different neural mechanisms. The dorsal visual pathway (i.e., inferior parietal cortex) would be more important in the processing of visuospatial information in peripersonal space, whereas the ventral visual pathway (i.e., superior and medial temporal cortex) would be more important in the processing of visuospatial information in extrapersonal space. Evidence for this hypothesis has been found in transcranial magnetic stimulation (TMS) and brain imaging studies in healthy subjects (Bjoertomt, Cowey, & Walsh, 2002; Lane, Ball, Smith, Schenk, & Ellison, 2013; Weiss et al., 2000). A preliminary study regarding the anatomy of peripersonal and extrapersonal neglect in right brain-damaged patients, mainly found shared anatomical substrates (Aimola et al., 2012).

Different types of neglect assessment are associated with different visuospatial mechanisms. Line bisection tasks draw on allocentric (object-based) representations, whereas cancellation tasks are egocentric (relative to the body of the individual) (Chechlacz et al., 2010; Ferber & Karnath, 2001; Karnath & Rorden, 2012; Molenberghs, Sale, & Mattingley, 2012). Although both tasks are sensitive to deficits in lateralized attention, several group studies clearly showed that double dissociations exist (e.g., Binder, Marshall, Lazar, Benjamin, & Mohr, 1992; Ferber & Karnath, 2001). Following from that, different brain regions are associated with performance on cancellation and bisection tasks (Binder et al., 1992; Daini, Angelelli, Antonucci, Cappa, & Vallar, 2002; Karnath et al., 2004; Karnath & Rorden, 2012; Molenberghs et al., 2012; Rorden, Fruhmann Berger, & Karnath, 2006). Investigating brain regions that relate with performance on one particular task is, therefore, a more fruitful approach to unravel neural substrates compared to the use of multiple tasks (Malhotra & Russell, 2015).

In the current study, we used continuous voxel-based lesion-symptom mapping (VLSM) to evaluate brain regions associated with neglect in peripersonal versus extrapersonal space. We performed analyses separately for neglect as measured with cancellation and line bisection tasks, as these tasks measure different aspects of lateralized attention. This method takes into account the severity of neglect. As there is no golden standard for the threshold of neglect, and differences in used thresholds exist among studies, using continuous outcome measures contributes to comparability between studies (Molenberghs et al., 2012). In order to accurately represent a stroke population, the current study included a large group of patients with left as well as right hemisphere brain damage. Knowledge about the dissociation between region-specific types of neglect, as measured with different tasks, gains insight into the neglect syndrome, which could aid diagnosis and treatment of neglect.

Material and methods

Participants

Patients were retrospectively selected from a cohort of stroke patients who were consecutively admitted to De Hoogstraat Rehabilitation centre in the period between

October 2011 and January 2017. MRI and CT scans were obtained as standard care at admission to the hospital. Patients received a neuropsychological neglect assessment as standard care within the first two weeks after admission to the rehabilitation centre. For the current study, we included stroke patients (first or recurrent) with data of the neglect screening for both regions of space (peripersonal and extrapersonal) for at least one neuropsychological neglect task (shape cancellation or line bisection). The following inclusion criteria were applied: (1) ischemic stroke or delayed cerebral ischemia after subarachnoid haemorrhage; and (2) delayed CT (i.e., performed <48 hours after symptom onset) or MRI brain scan available for infarct segmentation. Patients with a CT or MRI scan of insufficient quality were excluded from analyses. The research procedures were performed in accordance with the standards of the Declaration of Helsinki.

Demographic and stroke characteristics

The following data were obtained on admission to the rehabilitation centre: age, sex, time post-stroke onset, stroke history (first, recurrent), stroke type (ischemic, subarachnoid haemorrhage), and lesion side (left, right, bilateral). Lesion volume was computed based on the CT or MRI scan. Global cognitive functioning was screened with either the Mini-Mental State Examination (MMSE; Folstein et al., 1975) or the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). We converted MMSE scores into MoCA scores to create a single, pooled MoCA score. We applied the following formula: MoCA = (1.124 * MMSE) – 8.165 (Solomon et al., 2014). In addition, language communication deficits (Stichting Afasie Nederland; SAN score; Deelman et al., 1981), level of independence during daily live activities (Barthel Index; Collin et al., 1988), and strength in both upper and lower extremities (Motricity Index; Collin & Wade, 1990) were assessed.

Tasks and stimuli

In order to determine the presence of peripersonal and extrapersonal neglect, we used an experimental set-up with computerized versions of the shape cancellation and line bisection task, in accordance to the one used by Van der Stoep et al. (2013). The monitor was placed at a distance of 30 cm in the peripersonal, and at 120 cm in the extrapersonal space condition. Stimuli were enlarged in the extrapersonal condition to correct for visual angle. The region of space in which the tasks were presented first, was counterbalanced between patients. The shape cancellation task was always presented first followed by the line bisection task, in the same region of space.

Shape cancellation

Shape cancellation data was collected in between October 2011 and August 2014. The task consisted of 54 targets among 75 distractors. Patients had to click on targets using a computer mouse. After each click, a small circle appeared on the computer screen at the clicked location. There was no time limit. The difference in number of omissions between the left and right side of the stimulus field was computed (omission difference score). An omission difference score of ≥2 was used as an indication of neglect (Van der Stoep et al., 2013). Based on the amount and location of missed targets, the horizontal normalized centre of cancellation (CoC-x) was computed as a measure for severity of the lateralized attention deficit (Binder et al., 1992; Rorden & Karnath, 2010). The absolute CoC-x ranges from 0 (no neglect) up to 1 (severe neglect).

Line bisection

Line bisection data was collected in between October 2011 and January 2017. The task consisted of four trials with each three horizontal lines (approximately 22° long and 0.2° thick). The upper line was located in the right corner, the middle line in the middle, and the lower line in the left corner. There was a 28% vertical shift and a 15% horizontal shift with respect to the line length. Patients had to click on the subjective midpoint of each line, starting with the upper line working their way down. Per line, the average deviation was computed, resulting in a deviation score ranging from −11° to 11°. Patients with deviation scores outside the range of the performances of 28 healthy control subjects (as described in the study of Van der Stoep et al., 2013) on ≥2 lines, were allocated to one of the neglect groups. Subsequently, the deviation scores were absolutized, to obtain a continuous overall deviation score ranging from 0 (no neglect) to 11° (severe neglect).

Generation of lesion maps

The procedure for the generation of lesion maps has been previously described elsewhere (Biesbroek et al., 2016; Biesbroek, van Zandvoort, Kappelle, et al., 2014; Biesbroek, van Zandvoort, Kuijf, et al., 2014; Ten Brink, Biesbroek, et al., 2016), and is only summarised here. A trained rater (JMB) who was blinded to the behavioural data manually segmented infarcts on transversal slices of either follow-up CT (n = 70), or on T2 FLAIR sequences of MRI scans (n = 64). Infarct segmentations were transformed to the Montreal Neurological Institute (MNI)-152 template (Fonov et al., 2009). Quality checks of the registration results were performed by comparing the native scan to the lesion map in MNI space. For 65 patients, the co-registered lesion maps were manually adjusted to correct for slight registration errors using MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html) by JMB.

Statistical analysis

Results of the two tasks (i.e., shape cancellation and line bisection) were analysed separately.

Demographic and stroke characteristics

Patients were allocated to one of four groups: no neglect, peripersonal neglect, extrapersonal neglect, or neglect for both regions of space. Demographic and stroke characteristics were compared using a Kruskal-Wallis test (level of alpha = .05). In case of significant results between four groups, post-hoc Mann-Whitney analyses were performed with a Bonferroni correction for multiple testing (p = .008).

Lesion analyses

We used hypothesis-free VLSM to determine the relationship between task performance in peripersonal or extrapersonal space and the presence of a lesion in a given voxel (Rorden & Karnath, 2004). The absolute CoC-x (shape cancellation) and overall deviation score (line bisection) obtained in peripersonal and extrapersonal space conditions were introduced as continuous outcome measures. VLSM was performed using non-parametric mapping (Rorden, Bonilha, & Nichols, 2007; settings: t-test, univariate analysis, only including voxels that were damaged in at least five patients), before and after adjusting for total lesion volume. Correction for multiple testing was performed using a false discovery rate threshold (FDR) with $q < .05$. We additionally provided qualitative lesion overlay plots.

In addition, we performed region of interest (ROI)-based linear regression analyses, to quantify the impact of lesion volumes in specific regions on neglect severity. We extracted 96 cortical and 21 subcortical non-overlapping regions from the probabilistic Harvard-

Oxford atlas (threshold at .25; Desikan et al., 2006). Regions for subdivisions of gyri were merged into a single variable, thereby reducing the total number of regions to 89. In addition, we extracted regions for 16 white matter tracts from the probabilistic Johns Hopkins University White Matter Tractography Atlas (threshold at .25; Hua et al., 2008). All regions were projected on the VLSM results and the amount of voxels with a statistically significant correlation within each region was quantitatively assessed. Regions were considered to be related with neglect when at least 5% of tested voxels was statistically significant associated, with a total of no less than 100 significant voxels. For each patient, the lesion volumes within these ROIs were computed and entered as independent variables in a linear regression model, with the CoC-x or average deviation score as dependent variable, after adding total lesion volume to the model.

Results

Of 705 patients, 134 patients were included, of whom 98 completed the shape cancellation task and 129 the line bisection task in both regions of space (Figure 3.1). The most important reason for exclusion was the absence of a CT or MRI scan.

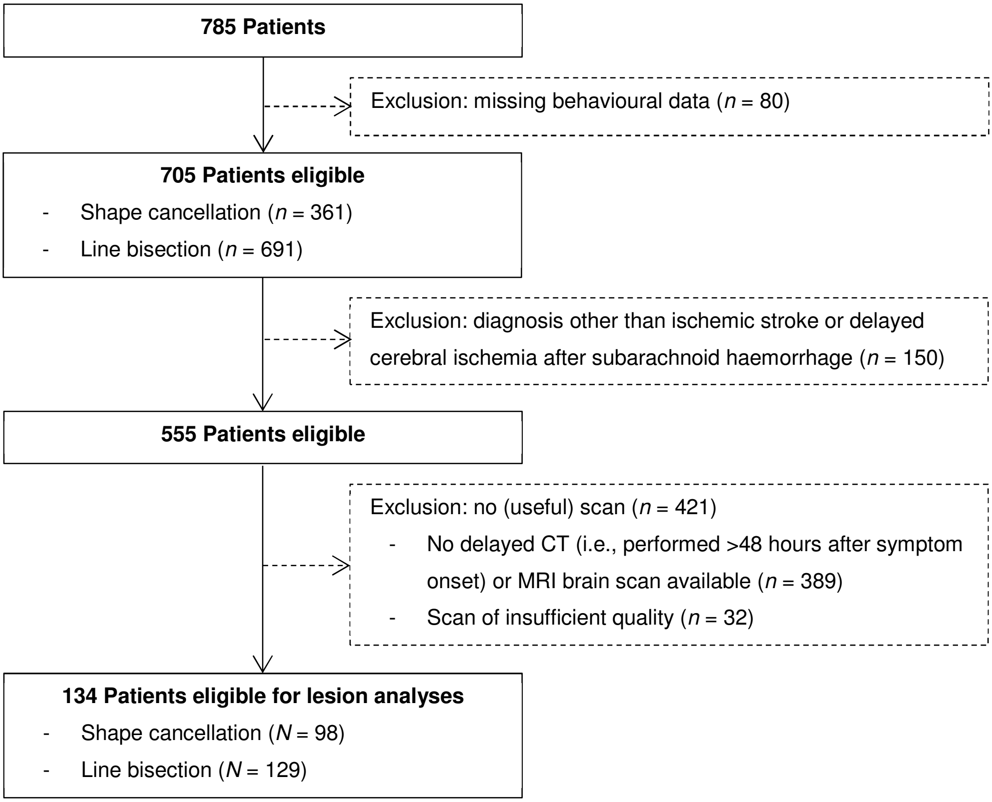


Figure 3.1 Flowchart of patient inclusion

Shape cancellation

Demographic and stroke characteristics

Of patients who performed the shape cancellation task, 69.4% did not show neglect, 8.2% showed neglect in peripersonal space, 8.2% in extrapersonal space, and 14.3% in both regions of space. Demographic and stroke characteristics are provided in Table 3.1.

Table 3.1 Demographic and stroke characteristics, median (interquartile range) or percentage split per group. Groups are based on the shape cancellation task (N = 98[1]).

	No neglect		Peripersonal neglect		Extrapersonal neglect		Neglect for both regions of space			Significant post-hoc
Outcome	*N*	*Mdn (IQR)*	*N*	*Mdn (IQR)*	*N*	*Mdn (IQR)*	*N*	*Mdn (IQR)*	Statistics	comparisons
Age (years)	68	58 (20)	8	61 (16)	8	57 (13)	14	50 (25)	$\chi^2(3) = 3.51$, $p = .320$	
Sex, % male	68	66.2%	8	50%	8	75%	14	57.1%	$\chi^2(3) = 1.53$, $p = .676$	
Time post-stroke (days)	68	22 (10)	8	33 (27)	8	40 (31)	14	32 (73)	$\chi^2(3) = 17.07$, $p = .001$	N-E, N-B
Stroke history, % first	61	91.8%	8	87.5%	8	87.5%	14	100%	$\chi^2(3) = 1.71$, $p = .635$	
Stroke type, % ischemic	68	94.1%	8	100%	8	100%	14	85.7%		
Lesion side	68		8		8		14		$\chi^2(3) = 2.67$, $p = .445$	
% Left		41.2%		50%		50%		7.1%		
% Right		47.1%		37.5%		50%		85.7%		
% Both		11.8%		12.5%		0%		7.1%		
Lesion volume (ml)	68	26 (73)	8	20 (81)	8	171 (140)	14	164 (228)	$\chi^2(3) = 21.10$, $p < .001$	N-E, N-B, P-B
MoCA	45	22 (5)	6	21 (6)	5	22 (4)	10	23 (2)	$\chi^2(3) = 3.21$, $p = .360$	
SAN	57	6 (2)	8	7 (1)	7	6 (6)	11	6 (1)	$\chi^2(3) = 4.43$, $p = .219$	
Barthel Index	55	15 (9)	7	13 (9)	7	12 (10)	11	8 (4)	$\chi^2(3) = 6.48$, $p = .091$	
Motricity Index arm	55	76 (61)	8	84 (24)	6	36 (79)	11	39 (84)	$\chi^2(3) = 6.33$, $p = .097$	
Motricity Index leg	54	91 (27)	8	84 (28)	6	70 (87)	11	58 (83)	$\chi^2(3) = 7.88$, $p = .049$	
Shape cancellation CoC-x	68		8		8		14			
Peripersonal space		.000 (.003)		.036 (.045)		.001 (.009)		.074 (.081)	$\chi^2(3) = 57.19$, $p < .001$	N-P, N-B, P-E, E-B
Extrapersonal space		.000 (.000)		.002 (.015)		.020 (.013)		.063 (.169)	$\chi^2(3) = 62.94$, $p < .001$	N-F, N-B, P-B, E-B

Abbreviations: B, neglect for both regions of space; CoC-x, horizontal center of cancellation; E, extrapersonal neglect; N, no neglect; MoCA, Montreal Cognitive Assessment; P, peripersonal neglect; SAN, Stichting Afasie Nederland.

[1]Group sizes differ per variable due to missing data.

Lesion analyses

In Figure 3.2A the spatial distribution of the voxels that were damaged in at least five patients are depicted.

VLSM for peripersonal neglect: The results of the VLSM analyses for the CoC-x in peripersonal space are depicted in Figure 3.2 (panels B and C). After correction for total lesion volume, the right parahippocampal gyrus, hippocampus, thalamus, cingulum of the hippocampus, and corticospinal tract were significant related with the CoC-x in peripersonal space (Figure 3.2C and Table 3.2).

VLSM for extrapersonal neglect: The voxels with an association between a lesion and a higher CoC-x in extrapersonal space are depicted in Figure 3.2 (panels D and E). Voxels within the right parahippocampal gyrus, hippocampus, thalamus, superior parietal lobule, angular gyrus, planum temporale, cingulum of the hippocampus, corticospinal tract, and to a lesser extent, supramarginal gyrus, lateral occipital cortex, superior temporal gyrus, and superior longitudinal fasciculus (temporal projections) remained significant after correction for total lesion volume (Figure 3.2E and Table 3.2). The qualitative lesion overlay plots are provided in Supplementary Figure 3.1.

ROI analyses for peripersonal neglect: In the linear regression model, we first added age and sex, and total lesion volume, which were not significantly associated with the CoC-x in peripersonal space (Table 3.3). The aforementioned regions were selected as ROIs, and their lesion volumes were included in the model. The increase in explained variance on top of age, sex and total lesion volume, was highest for lesion volume within the right parahippocampal gyrus (increase in explained variance of 26.4%; $p < .001$).

ROI analyses for extrapersonal neglect: When we inserted the CoC-x in extrapersonal space as dependent variable, age and sex were not significantly associated with extrapersonal neglect (Table 3.3). The total lesion volume explained an additional 6.1% ($p = .015$). The increase in explained variance on top of age, sex and total lesion volume was highest for lesion volume within the right thalamus (increase in explained variance of 20.9%; $p < .001$).

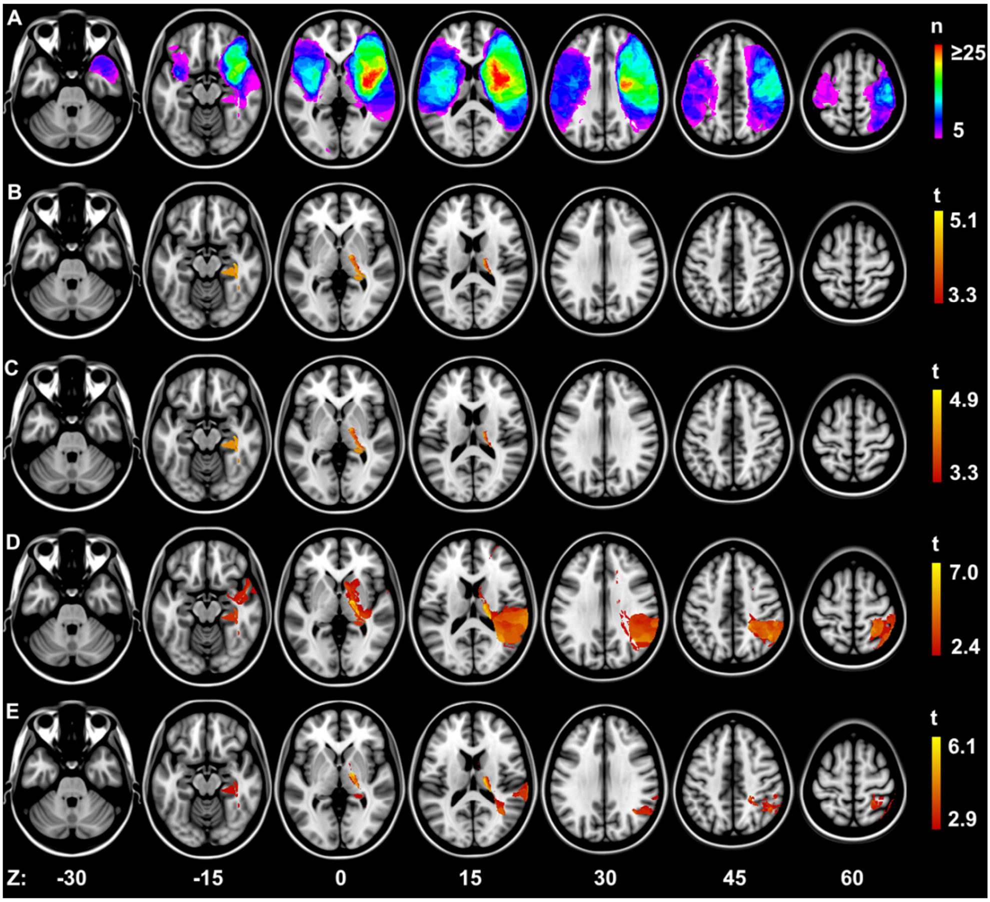


Figure 3.2 Distribution of ischemic lesions and VLSM results for the shape cancellation task (N = 98). The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. (A) Voxels that are damaged in at least five patients are plotted. The coloured bar indicates the number of patients with a lesion for a given voxel. Map of the voxel wise association (t-statistic) between the presence of a lesion and the absolute CoC-x value (B) in peripersonal space, (C) in peripersonal space adjusted for total lesion volume, (D) in extrapersonal space, (E) in extrapersonal space adjusted for total lesion volume. Voxels exceeding the FDR threshold (q = .05) are rendered on a scale from red to yellow.

Table 3.2 Voxel-based lesion-symptom mapping results for the **shape cancellation task**: **tested and significant voxels for each region after correction for total lesion volume.**

Anatomical regions	Patients with lesion (n)[a]	Region size in voxels (n)	Tested voxels (n)	Significant voxels in peripersonal space (n [%])	Significant voxels in extrapersonal space (n [%])
Grey matter					
R parahippocampal gyrus	15	7870	418	377 (90.19%)	377 (90.19%)
R hippocampus	15	5748	1369	1179 (86.12%)	1106 (80.79%)
R thalamus	29	10238	1891	1030 (54.47%)	1081 (57.22%)
R superior parietal lobule	21	11800	7851	0	2471 (31.47%)
R angular gyrus	20	11704	11588	0	3342 (28.84%)
R planum temporale	27	3538	3538	0	756 (21.37%)
R supramarginal gyrus	30	16304	16292	0	1778 (10.91%)
R lateral occipital cortex	23	54872	14700	0	1345 (9.15%)
R superior temporal gyrus	25	5509	5483	0	344 (6.27%)
White matter					
R cingulum of the hippocampus	5	798	195	195 (100%)	195 (100%)
R corticospinal tract	37	5021	3112	206 (6.62%)	483 (15.52%)
R superior longitudinal fasciculus (temporal projections)	31	1956	1929	0	133 (6.89%)

Abbreviation: R, right.

Note. Regions for which our criterion for involvement was met (i.e. ≥5% of tested voxels had a statistically significant association between the presence of a lesion and the CoC-x, with a minimum of 100 significant voxels) are shown here; the remaining regions are not shown.

Table 3.3 Results of linear regression models with CoC-x (shape cancellation task) in peripersonal and extrapersonal space as outcome after correction for total lesion volume.

		Peripersonal space			*Extrapersonal space*		
Model	Independent variables	R^2	$p\Delta R^2$	*B* (95% CI)	R^2	$p\Delta R^2$	*B* (95% CI)
1	Age, sex	.008	.685		.003	.864	
2	Model 1 + total lesion volume	.014	.454	.00 (.00 to .00)	.064	.015*	.00 (.00 to .00)
3a	Model 2 + R parahippocampal gyrus	.278	< .001*	.10 (.07 to .13)	.202	< .001*	.05 (.03 to .07)
3b	Model 2 + R hippocampus	.102	.003*	.05 (.02 to .08)	.110	.031*	.02 (.00 to .04)
3c	Model 2 + R thalamus	.242	< .001*	.06 (.04 to .09)	.273	< .001*	.04 (.02 to .05)
3d	Model 2 + R superior parietal lobule	-			.184	< .001*	.01 (.01 to .02)
3e	Model 2 + R angular gyrus	-			.213	< .001*	.01 (.01 to .02)
3f	Model 2 + R planum temporale	-			.169	.001*	.02 (.01 to .04)
3g	Model 2 + R supramarginal gyrus	-			.142	.005*	.01 (.00 to .01)
3h	Model 2 + R lateral occipital cortex	-			.080	.216	.00 (-.00 to .00)
3i	Model 2 + R superior temporal gyrus	-			.066	.649	.00 (-.01 to .01)
3j	Model 2 + R cingulum of the hippocampus	.242	< .001*	.34 (.21 to .47)	.187	< .001*	.16 (.07 to .24)
3k	Model 2 + R corticospinal tract	.028	.247	.02 (-.01 to .05)	.102	.051	.02 (.00 to .04)
3l	Model 2 + R superior longitudinal fasciculus (temporal projections)	-			.106	.041*	.03 (.00 to .06)

Abbreviation: R, right.

Note.The explained variance (R^2) of the CoC-x on the shape cancellation is given for each model with the corresponding *p*-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (*B*) applies to the change in CoC-x for every 1 ml increase in lesion volume, with higher CoC-x meaning more severe neglect.

*Statistically significant with an alpha-level of $p < .05$.

Line bisection

Demographic and stroke characteristics

Of patients who performed the line bisection task, 73.6% did not show neglect, 10.9% showed neglect in peripersonal space, 6.2% in extrapersonal space and 9.3% in both regions of space. Demographic and stroke characteristics are provided in Table 3.4.

Lesion analyses

In Figure 3.3A, the spatial distribution of the voxels that were damaged in at least five patients are depicted.

VLSM for peripersonal neglect: In Figure 3.3B, voxels that were significantly associated with performance at the line bisection in peripersonal space are presented. None of the voxels, however, remained significantly associated with neglect in peripersonal space after correction for total lesion volume (Figure 3.3C). In other words, this indicates that no specific brain regions were associated with peripersonal neglect as measured with the line bisection task.

VLSM for extrapersonal neglect: The results for the line bisection task in extrapersonal space are shown in Figure 3.3 (panels D and E). After correction for total lesion volume, multiple brain areas in the right hemisphere were significantly associated with the line bisection in extrapersonal space (Figure 3.3E and Table 3.5). Areas with most significant voxels were the right intracalcarine cortex, temporal fusiform cortex, precuneous cortex, lingual gyrus, temporal occipital fusiform cortex, occipital pole, hippocampus, parahippocampal gyrus, cuneal cortex, lateral occipital cortex, occipital fusiform gyrus, inferior temporal gyrus, and cingulum of the hippocampus. Qualitative overlay plots are provided in Supplementary Figure 3.2.

ROI analyses for extrapersonal neglect: We first added age and sex, which were not significantly related with the deviation in extrapersonal space (Table 3.6). Subsequently, total lesion volume was added, which explained an additional 15.7% in variance ($p < .001$). The increase in explained variance on top of age, sex and total lesion volume was highest for lesion volume within the right temporal fusiform cortex (increase in explained variance of 34.2%; $p < .001$).

Table 3.4 Demographic and stroke characteristics, median (interquartile range) or percentage split per group. Groups are based on the **line bisection task** (*N* = 129[1]).

Outcome	No neglect		Peripersonal neglect		Extrapersonal neglect		Neglect for both regions of space		Statistics	Significant post-hoc comparisons
	N	*Mdn*	*N*	*Mdn*	*N*	*Mdn*	*N*	*Mdn*		
Age (years)	95	54 (20)	14	62 (27)	8	68 (19)	12	64 (16)	$\chi^2(3) = 4.63$, $p = .201$	
Sex, % male	95	62.1%	14	71.4%	8	50.0%	12	83.3%	$\chi^2(3) = 3.12$, $p = .374$	
Time post-stroke (days)	95	23 (16)	14	23 (12)	8	21 (11)	12	25 (43)	$\chi^2(3) = 1.45$, $p = .694$	
Stroke history, % first	85	87.1%	14	85.7%	7	100%	9	100%	$\chi^2(3) = 2.39$, $p = .495$	
Stroke type, % ischemic	95	94.7%	14	100%	8	87.5%	12	100%	$\chi^2(3) = 2.46$, $p = .483$	
Lesion side	95		14		8		12		$\chi^2(3) = 3.46$, $p = .750$	
% Left		34.7%		28.6%		50.0%		33.3%		
% Right		46.3%		57.1%		50.0%		58.3%		
% Both		18.9%		14.3%		0%		8.3%		
Lesion volume (ml)	95	31.7 (104.2)	14	26.2 (139.0)	8	28.2 (126.5)	12	90.3 (206.5)	$\chi^2(3) = 5.45$, $p = .142$	
MoCA	67	23 (3)	11	22 (7)	5	20 (3)	4	22 (3)	$\chi^2(3) = 6.05$, $p = .109$	
SAN	81	6 (2)	13	6 (2)	6	6 (2)	9	5 (2)	$\chi^2(3) = 1.93$, $p = .587$	
Barthel Index	79	14 (9)	11	7 (5)	6	15 (9)	9	12 (11)	$\chi^2(3) = 6.50$, $p = .090$	
Motricity Index arm	79	76 (75)	12	73 (88)	6	80 (25)	10	61 (80)	$\chi^2(3) = 4.26$, $p = .235$	
Motricity Index leg	78	83 (36)	12	87 (89)	6	96 (13)	10	75 (100)	$\chi^2(3) = 3.50$, $p = .320$	
Line bisection, deviation	95		14		8		12			
Peripersonal space		0.31 (0.29)		0.89 (0.42)		0.62 (0.42)		1.20 (1.65)	$\chi^2(3) = 57.41$, $p < .001$	N-P, N-B, F-B
Extrapersonal space		0.40 (0.30)		0.41 (0.38)		1.27 (0.53)		1.84 (1.79)	$\chi^2(3) = 44.97$, $p < .001$	N-F, N-B, N-F, N-B

Abbreviations: B, neglect for both regions of space; E, extrapersonal neglect; N, no neglect; MoCA, Montreal Cognitive Assessment; P, peripersonal neglect; SAN, Stichting Afasie Nederland. [1] Group sizes differ per variable due to missing data.

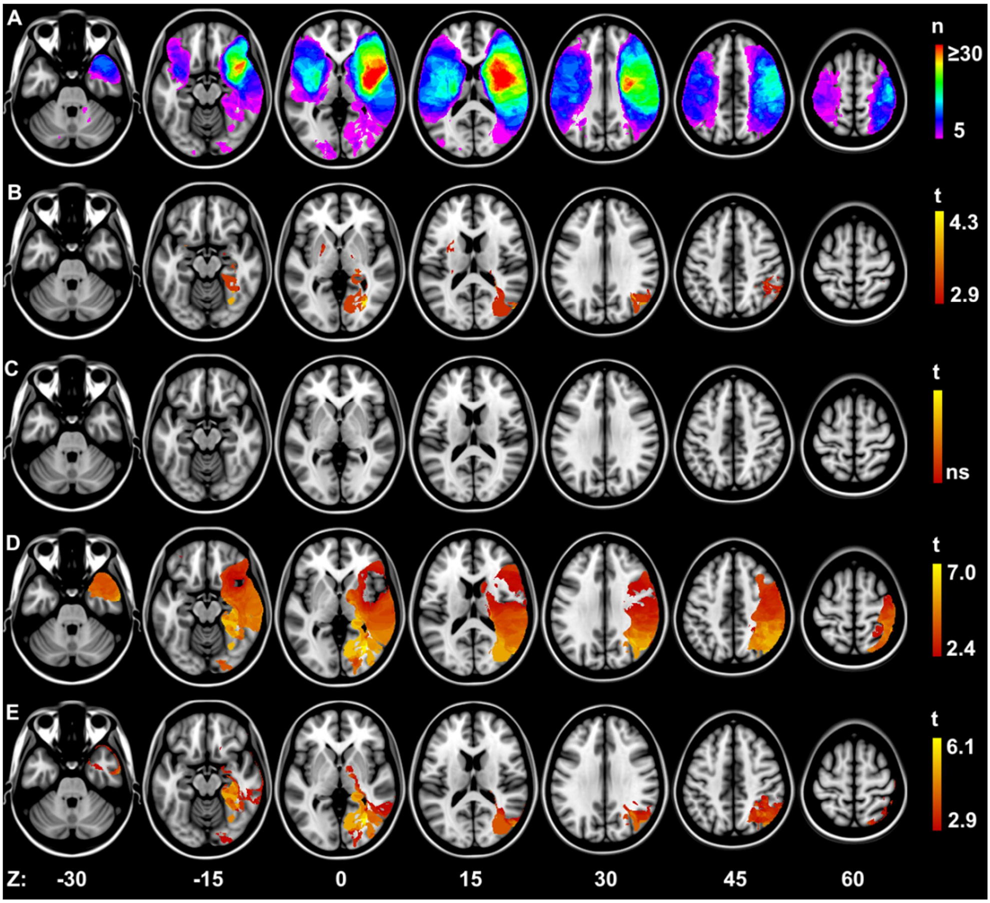


Figure 3.3 Distribution of ischemic lesions and VLSM results for the line bisection task (*N* = 129). The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. (A) Voxels that are damaged in at least five patients are plotted. The coloured bar indicates the number of patients with a lesion for a given voxel. Map of the voxel wise association (*t*-statistic) between the presence of a lesion and the absolute deviation (B) in peripersonal space, (C) in peripersonal space adjusted for total lesion volume, (D) in extrapersonal space, (E) in extrapersonal space adjusted for total lesion volume. Voxels exceeding the FDR threshold (q = .05) are rendered on a scale from red to yellow.

Table 3.5 Voxel-based lesion-symptom mapping results for the **line bisection task in extrapersonal space**: tested and significant voxels for each region after correction for total lesion volume. Note that none of the tested regions were significantly associated with deviation on the line bisection in peripersonal space.

Anatomical regions	Patients with lesion (n)[a]	Region size in voxels (n)	Tested voxels (n)	Significant voxels in extrapersonal space (n [%])
Grey matter				
R intracalcarine cortex	10	5993	181	181 (100%)
R temporal fusiform cortex	20	8041	1010	1008 (99.80%)
R precuneous cortex	17	22854	261	260 (99.62%)
R lingual gyrus	14	13917	5162	5058 (97.99%)
R temporal occipital fusiform cortex	15	6603	3011	2939 (97.61%)
R occipital pole	14	19603	1838	1723 (93.74%)
R hippocampus	18	5748	2278	2090 (91.75%)
R parahippocampal gyrus	21	7870	1686	1537 (91.16%)
R cuneal cortex	9	5063	387	344 (88.89%)
R lateral occipital cortex	33	54872	28083	23358 (83.18%)
R occipital fusiform gyrus	10	7137	2986	2431 (81.41%)
R inferior temporal gyrus	19	16601	2671	2009 (75.22%)
R amygdala	28	2847	1850	902 (48.76%)
R angular gyrus	30	11704	11685	4145 (35.47%)
R thalamus	33	10238	2230	519 (23.27%)
R middle temporal gyrus	23	20577	13858	2688 (19.40%)
R superior parietal lobule	31	11800	8960	1667 (18.60%)
R temporal pole	36	18965	16297	2729 (16.75%)
R supramarginal gyrus	40	16304	16303	999 (6.13%)
White matter				
R cingulum of the hippocampus	7	798	521	521 (100%)
Forceps major	24	6529	735	491 (66.80%)
R inferior longitudinal fasciculus	34	8153	3771	1803 (47.81%)
R inferior fronto-occipital fasciculus	53	7880	7320	1825 (24.93%)
R corticospinal tract	51	5021	3124	245 (7.84%)

Abbreviation: R, right.

Note. Regions for which our criterion for involvement was met (i.e. ≥5% of tested voxels had a statistically significant association between the presence of a lesion and the deviation on the line bisection, with a minimum of 100 significant voxels) are shown here; the remaining regions are not shown.

[a] Indicates how many of the 129 patients had a lesion (≥1 voxel) within the specified region.

Table 3.6 Results of linear regression models with deviation (line bisection task) in extrapersonal space as outcome after correction for total lesion volume.

		Extrapersonal space		
Model	Independent variables	R^2	$p\Delta R^2$	*B* (95% CI)
1	Age, sex	.018	.312	
2	Model 1 + total lesion volume	.175	< .001*	.00 (.00 to .01)
3a	Model 2 + R intracalcarine cortex	.311	< .001*	.38 (.23 to .53)
3b	Model 2 + R temporal fusiform cortex	.517	< .001*	.64 (.50 to .77)
3c	Model 2 + R precuneous cortex	.194	.089	.06 (-.01 to .14)
3d	Model 2 + R lingual gyrus	.342	< .001*	.18 (.12 to .25)
3e	Model 2 + R temporal occipital fusiform cortex	.307	< .001*	.33 (.20 to .46)
3f	Model 2 + R occipital pole	.289	< .001*	.15 (.08 to .21)
3g	Model 2 + R hippocampus	.375	< .001*	.56 (.38 to .73)
3h	Model 2 + R parahippocampal gyrus	.507	< .001*	.76 (.60 to .93)
3i	Model 2 + R cuneal cortex	.277	< .001*	.41 (.22 to .61)
3j	Model 2 + R lateral occipital cortex	.368	< .001*	.06 (.04 to .08)
3k	Model 2 + R occipital fusiform gyrus	.308	< .001*	.31 (.18 to .44)
3l	Model 2 + R inferior temporal gyrus	.417	< .001*	.26 (.19 to .33)
3m	Model 2 + R amygdala	.275	< .001*	.69 (.36 to 1.02)
3n	Model 2 + R angular gyrus	.255	< .001*	.11 (.05 to .16)
3o	Model 2 + R thalamus	.193	.095	.18 (-.03 to .40)
3p	Model 2 + R middle temporal gyrus	.288	< .001*	.10 (.06 to .15)
3q	Model 2 + R superior parietal lobule	.202	.042*	.08 (.00 to .15)
3r	Model 2 + R temporal pole	.225	.005*	.05 (.02 to .09)
3s	Model 2 + R supramarginal gyrus	.204	.034*	.05 (.00 to .09)
3t	Model 2 + R cingulum of the hippocampus	.362	< .001*	2.80 (1.88 to 3.71)
3u	Model 2 + Forceps major	.248	.001*	.53 (.23 to .83)
3v	Model 2 + R inferior longitudinal fasciculus	.350	< .001	.61 (.40 to .81)
3w	Model 2 + R inferior fronto-occipital fasciculus	.200	.052	.12 (00 to .24)
3x	Model 2 + R corticospinal tract	.175	.876	-.02 (-.26 to .22)

Abbreviation: R, right.

Note. The explained variance (R^2) of the deviation on the line bisection is given for each model, with the corresponding *p*-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (*B*) applies to the change in CoC-x for every 1 ml increase in lesion volume, with higher deviation meaning more severe neglect.

*Statistically significant with an alpha-level of $p < .05$.

Discussion

Our aim was to unravel neural substrates of peripersonal and extrapersonal neglect by applying VLSM analyses. To address this aim, analyses were performed for digitized shape cancellation and bisection tasks separately, in two large samples of 98 and 129 stroke patients, respectively. Both patients with left- and right hemispheric damage were included to represent a general stroke population.

We hypothesised that ventral areas (e.g., superior and medial temporal cortex), previously related with recognition and representation of objects and scenes, would be related with extrapersonal spatial attention (Lane et al., 2013; Previc, 1998), and that dorsal areas (e.g., inferior parietal cortex), which play a role in perception for action, would be related with peripersonal spatial processing, since a person can potentially interact directly with information in peripersonal space (Lane et al., 2013).

When neglect was measured with the shape cancellation task, the right parahippocampal gyrus, hippocampus, thalamus, cingulum of the hippocampus, and corticospinal tract were associated with neglect in both peripersonal and extrapersonal space. Additionally, the right superior parietal lobule, angular gyrus, supramarginal gyrus, and planum temporale, and to a lesser extent, the right lateral occipital cortex, superior temporal gyrus, and superior longitudinal fasciculus (temporal projections) were related to neglect in extrapersonal space. No additional brain areas were related to neglect in peripersonal space.

With respect to the line bisection task, a relation was found between extrapersonal neglect and the right parahippocampal gyrus, hippocampus, thalamus, superior parietal lobule, angular gyrus, supramarginal gyrus, precuneous cortex, several structures in the occipital (i.e., lateral occipital cortex, occipital pole, lingual gyrus, occipital fusiform gyrus, and cuneal cortex) and temporal lobes (i.e., temporal pole, middle temporal gyrus, inferior temporal gyrus, temporal fusiform cortex, and temporal occipital fusiform cortex), intracalcarine cortex and several white matter tracts (i.e., cingulum of the hippocampus, forceps major, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract). No brain areas were significantly related with neglect in peripersonal space.

With respect to the ventral/dorsal association hypothesis, we found that lesions in the right parahippocampal gyrus, hippocampus, and superior temporal gyrus (ventral areas), were indeed associated with neglect in extrapersonal space, however, the parahippocampal gyrus and hippocampus were *also* associated with peripersonal neglect. In addition, we found an association between lesions in dorsal areas (i.e., the supramarginal gyrus and angular gyrus) and extrapersonal neglect only. In other words, our results do not fit the ventral/dorsal hypothesis.

There is only one other study regarding lesion symptom mapping on this topic (Aimola et al., 2012). They did report associations between specific brain areas associated with peripersonal neglect only versus extrapersonal neglect only. One explanation for the discrepancy between these studies could be the methodological differences between the study of Aimola et al. (2012) and ours. First, in their study, the peripersonal and extrapersonal neglect groups consisted of only four patients, and, furthermore, no correction factors, such as lesion volume or including only voxels that are damaged in a minimum number of patients, were applied (Sperber & Karnath, 2017). Thus, brain areas that would have been (coincidentally) damaged in only one of these patients, could immediately show up as being related to region-specific neglect in their lesion subtraction analyses. There is, therefore, a relatively high probability of false positive findings in the study of Aimola et al. (2012).

Another methodological difference is response type, which might (partly) explain differences between our study and the study of Aimola et al. (2012). In their study, patients made direct contact with the targets in peripersonal space (i.e., through the use of a pencil), whereas a laser pointer was used in extrapersonal space. This difference in response type could possibly explain different brain areas that were found to be involved with task performance. When there is sensory continuity between the patient and target, as is the case with a rod for example, the tool is coded as part of the patient’s hand and extrapersonal space may be ‘remapped’ into peripersonal space (Adair & Barrett, 2008; Berti & Frassinetti, 2000). Stated differently by Neppi-Mòdona et al. (2007); “Tool use can make an object nearer or farther depending on the presence/absence of contact between the object and the agent’s body”. In the current study, both conditions (i.e., peripersonal versus extrapersonal) required the same type of (motor) response, with no contact between stimuli and the patient. We can, therefore, make neat direct comparisons between the two distances at which the stimuli were presented to the patients, yet we cannot compare differences between 'action space' and 'orientation space'. Our VLSM results therefore indicate the associated brain areas with attention processing of visual stimuli in two regions of space, but we cannot make statements on associations between regions of space, response types, and neglect (which was also not the aim of the current study). These differences in response type might, however, have serious impact on the associated brain areas.

Limitations

It is now generally accepted that focal lesions can have devastating remote effects on the function of distant brain regions via white matter tracts (Carey et al., 2013; Finger, Koehler, & Jagella, 2004). The consequences of a lesion are determined by both lesion volume and the specific lesion location. Lesions in, for example, white matter tracts can have more severe remote consequences than cortical lesions. With respect to neglect, this disorder is assumed to be the consequence of changes in the overall frontoparietal network rather than from a single lesioned area (Carey et al., 2013; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). We, therefore, included ROIs for the major fibre pathways in our ROI-based analyses. Unfortunately, we had no access to more advanced measures, regarding the orientation and anisotropy of white matter tracts, which can be estimated with diffusion tensor imaging (DTI).

Furthermore, we did not exclude patients with occipital lesions or visual field defects. There is debate regarding whether this patient group should be excluded in order to include only patients with 'pure' spatial neglect. However, an important patient group will then be missed, as patients with posterior damage often show neglect and will be underrepresented in the sample (Mort, 2003). In addition, it has been shown that visual field defects from an isolated occipital lesion do not cause neglect (Park et al., 2006), and would, therefore, not affect results.

Only right brain areas were associated with visuospatial neglect in this cohort, even though we included stroke patients with both left and right brain damage. Neglect following right brain damage is more frequent and severe (Chen, Chen, et al., 2015; Gainotti et al., 1972; Ten Brink, Verwer, et al., 2017), which might be the cause of this finding. Alternatively, severe deficits in understanding, as part of aphasia, led to missing data. Typically, these deficits are associated with the left hemisphere. On the other hand, we have included a large, unselected sample of stroke patients compared to other lesion studies. Our sample, therefore, is more representative for a general stroke population compared to other studies.

Future directions and conclusions

This study identified several right temporal and thalamic regions that are related to both peripersonal and extrapersonal neglect, and several additional right temporal, parietal and occipital regions that were specifically related to extrapersonal neglect. Our results only partly fit the dorsal/ventral hypothesis. Most importantly, we found several overlapping brain regions for neglect in peripersonal versus extrapersonal space, suggesting that lateralized attention for different regions of space largely relies on the *same* brain areas.

Methodological differences between studies regarding neural substrates of neglect likely explain discrepant findings between studies. For example, it could relate to the response type (i.e., contact or no contact with the stimuli) that was required in peripersonal and extrapersonal space conditions. Future studies could aim to disentangle both the quality of processing visual information in different regions of space as well as pinpoint the impact of different interaction styles in different regions of space. Furthermore, variations exist with respect to inclusion criteria (mostly right-brain damaged patients without severe language deficits), sample size (small groups), time post-stroke onset, used tasks and thresholds to define neglect, scan techniques (CT versus MRI), and correction factors (e.g., lesion volume). We will discuss some of these issues and make suggestions for future research regarding neural substrates of (region-specific) visuospatial neglect.

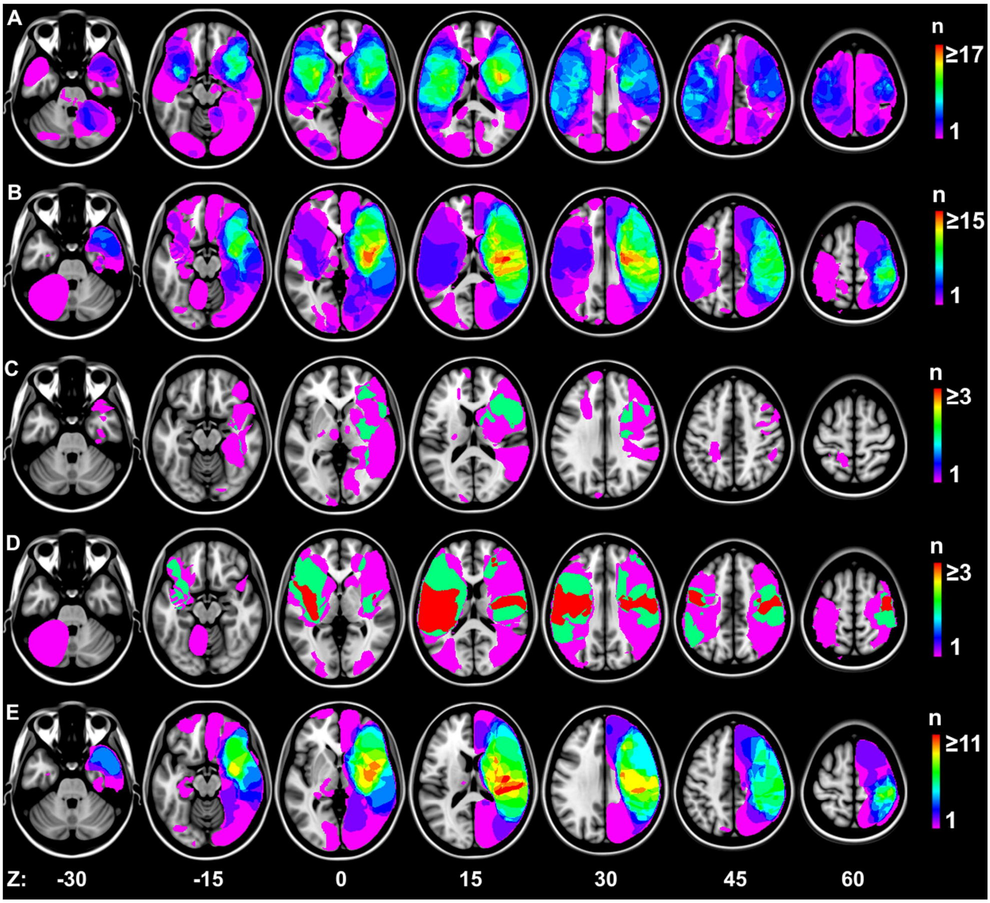
An important issue in neglect research is the time post-stroke onset. In the current study, brain scans were made at admission to the hospital (that is, within the first days post-stroke onset), whereas the neglect tasks were administered around 1 month post-stroke onset. In the first three months post-stroke onset, most of the spontaneous neurobiological recovery takes place (Nijboer, Kollen, et al., 2013). Immediately after stroke, for example, the blood supply to several brain areas can be distorted, leading to temporarily dysfunction of the visuospatial attention system. Brain areas that are related to visuospatial attention processes, however, could still be structurally intact. Measuring neglect immediately after stroke, and relate this behaviour to lesion locations would, therefore, not enhance insight, as patients *without* lesions in relevant areas could also show neglect, due to the aforementioned temporarily dysfunction. A solution for this issue would be the evaluation of functional networks instead of lesion locations alone. In this way, physiological changes in structural intact distant areas that possibly relate to visuospatial attention can be revealed. Although lesion studies are a first step to gain insight into the potentially affected (key) brain areas related to neglect subtypes, insights into the remote effects of such lesions are crucial to fully understand attentional processes. In the future, focus should, therefore, be on (the recovery of) functional brain networks (Corbetta et al., 2005).

Furthermore, improved performances over time could be due to a lack of *sensitivity* of the tasks that were used and/or learning or strategic effects (Appelros et al., 2003; Ten Brink, Visser-Meily, & Nijboer, 2017). Paper-and-pencil tasks are largely 'static', there is little interference of distractors, and patients can focus on one goal. In such tasks, some neglect patients could apply compensatory strategies, mimicking 'normal' performances, while neglect is still present in daily activities. Dynamic multitasks for neglect are more sensitive and less affected by compensatory strategies. Using such tasks, therefore, could improve detection of neglect patients. In addition, studies regarding the neural substrates of neglect should focus on *specific* neglect tasks (i.e., no test batteries or combined scores), to be able to draw conclusions regarding specific types of behaviour. Examples are computerized tasks, with a component of timing (e.g., Temporal Order Judgement; Van der Stigchel & Nijboer, 2017) or dual-tasking (Blini et al., 2016; Bonato, Priftis, Umiltà, & Zorzi, 2013). Such tasks could be administered in two regions of space, to measure peripersonal versus extrapersonal neglect. Furthermore, the *severity* of neglect should be taken into account (i.e., use a continuous measure). In this case, no (arbitrary) threshold has to be used, which enhances comparability between studies.

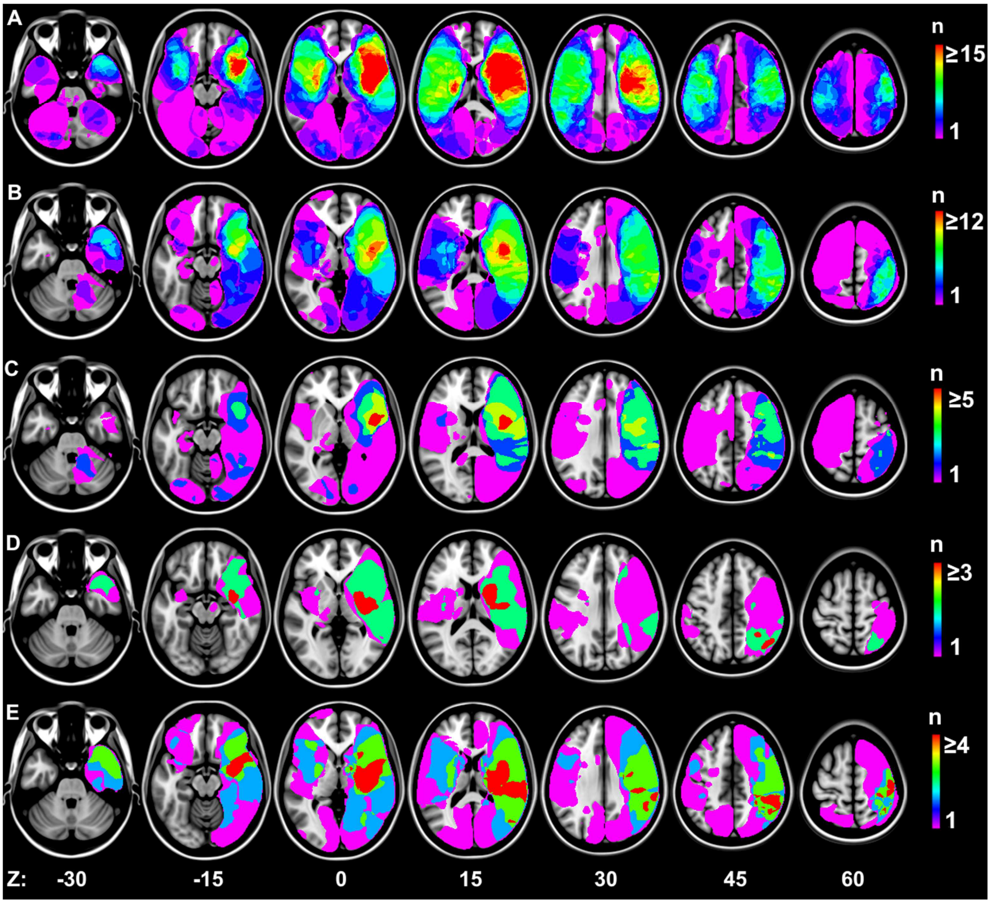
Finally, in most neglect studies, only patients with right hemispherical damage have been included. Neglect could, however, also occur following left hemispherical damage (Chen, Chen, et al., 2015; Gainotti et al., 1972; Ten Brink, Verwer, et al., 2017). As differences exist regarding frequency, severity, and region-specify in left- versus right-sided neglect (Ten Brink, Verwer, et al., 2017), possibly, neural substrates are not comparable, and should be evaluated separately. In order to do so, large samples of unselected stroke patients should be included.

Acknowledgements

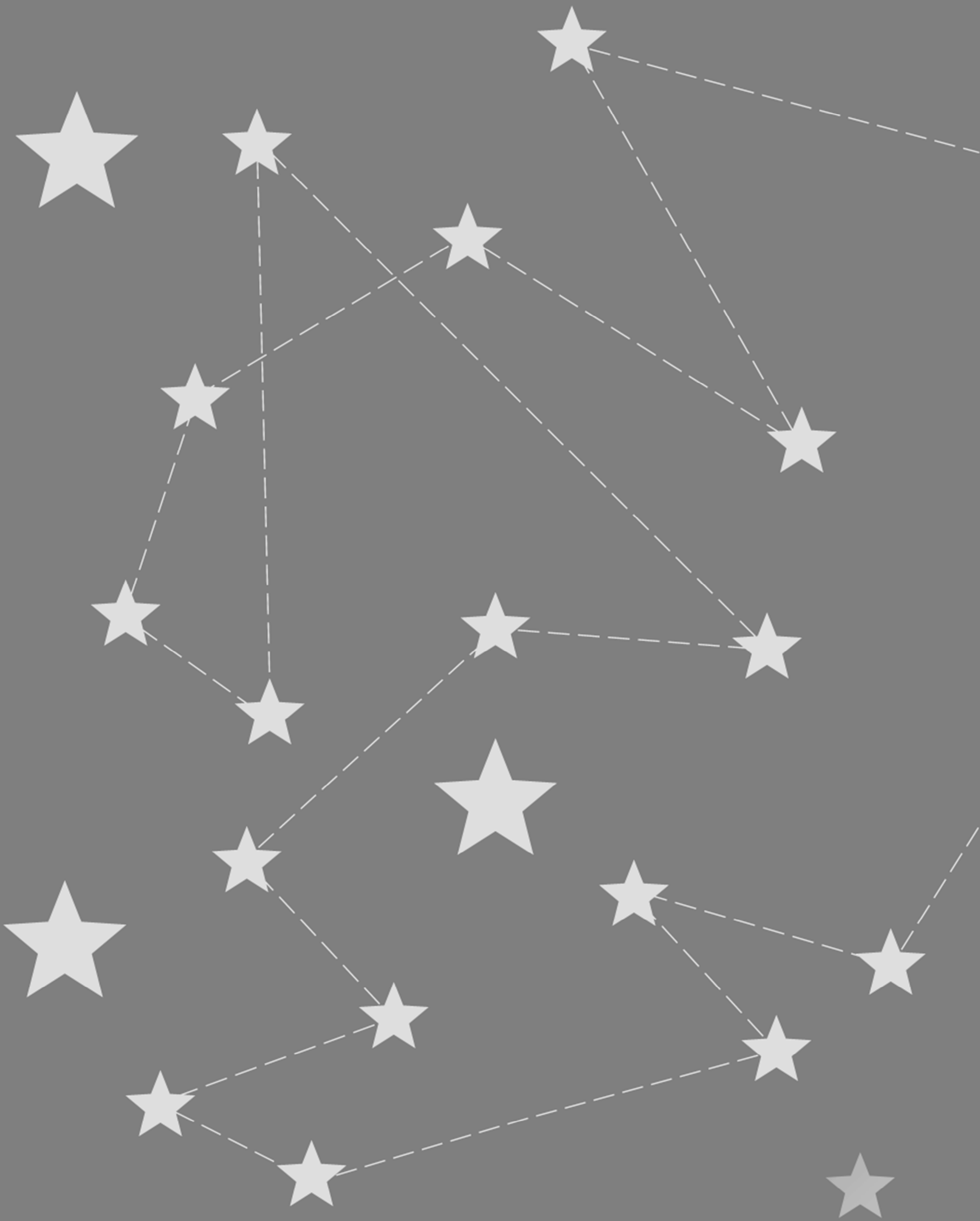
This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN, and the “Revalidatiefonds” under grant R2012134 to TCWN and JMAVM. We would like to thank Krista Huisman, Jorine van der Pas, and Charlotte Pasma for their help in collecting the data, and dr. Hugo Kuijf for the registration of CT and MRI scans.



Supplementary Figure 3.1 Lesion overlay plots of groups based on performance at the shape cancellation task (*N* = 98). The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. The overlay plots show the number of patients with a lesion for a given voxel separately for patients (A) without neglect (*n* = 68), (B) any type of neglect (*n* = 30), (C) peripersonal neglect (*n* = 8), (D) extrapersonal neglect (*n* = 8), (E) and neglect in both regions of space (*n* = 14).



Supplementary Figure 3.2 Lesion overlay plots of groups based on performance at the line bisection task (*N* = 129). The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. The overlay plots show the number of patients with a lesion for a given voxel separately for patients (A) without neglect (*n* = 95), (B) any type of neglect (*n* = 34), (C) peripersonal neglect (*n* = 14), (D) extrapersonal neglect (*n* = 8), (E) and neglect in both regions of space (*n* = 12).



Part II

Sensitive diagnosis

Chapter 4

Dynamic assessment of visual neglect: The Mobility Assessment Course as a diagnostic tool

Ten Brink, A. F., Visser-Meily, J. M. A., Nijboer, T. C. W. (In press). Dynamic assessment of visual neglect: The Mobility Assessment Course as a diagnostic tool. *Journal of Clinical and Experimental Neuropsychology*.

Abstract

Introduction. Visual neglect is a frequent disorder following stroke and is often diagnosed by neuropsychological assessment. However, paper-and-pencil tasks have low predictive value as they lack sensitivity to capture neglect in complex, dynamic situations, such as activities of daily living. Aims of the current study were to assess the feasibility of the Mobility Assessment Course (MAC), a visual search multitask, to assess neglect, and its relation with existing neglect tasks. *Methods*. Stroke patients admitted for inpatient rehabilitation and healthy controls were tested with the MAC in different corridors. Participants had to move through a corridor, finding and reporting 24 targets attached to the walls. In addition, the shape cancellation, line bisection, and Catherine Bergego Scale (CBS) were used to compare the MAC with existing diagnostic tools for neglect. *Results*. Administering the MAC was feasible, as 112 of 113 patients completed the MAC with a median duration of 4.09 min. Depending on the corridor where the assessment took place, in 88.5 to 93.3% of assessments all targets were visible. The number of omissions (total and contralesional) and the asymmetry score (contralesional – ipsilesional omissions) on the MAC as well as collisions and corrections, were higher for patients with neglect than for those without neglect. Depending on the neglect task used, 4 to 18.6% of patients without neglect on neuropsychological tasks or the CBS showed neglect on the MAC. Vice versa, 17.2 to 29.3% of patients who showed neglect at neuropsychological assessment or the CBS did not do so on the MAC. Finally, a moderate to strong positive relation was seen between neglect at neuropsychological assessment, the CBS, and the MAC. *Conclusions*. The MAC is an ecological task in which both quantitative and qualitative data on neglect can be collected. To assess the presence of neglect and neglect severity in a dynamic way, the MAC could be administered in conjunction with neuropsychological assessment.

Introduction

One prominent deficit following stroke is visuospatial neglect (commonly referred to as neglect). Patients with neglect fail, or are much slower, to orient toward, respond to, and report stimuli that occur at the contralesional side of space. In the acute phase following a stroke, approximately 50% of patients with right-hemisphere damage and 30% of patients with left-hemisphere damage show neglect (Chen, Chen, et al., 2015). Within 3 months post-stroke onset, most recovery takes place; however, 40% of patients with neglect in the subacute phase shows neglect 1 year post-stroke onset (Nijboer, Kollen, et al., 2013). Neglect interferes with activities in daily life (Appelros et al., 2002) and is associated with poorer functional as well as motor recovery (Adams & Hurwitz, 1963; Nijboer, Kollen, et al., 2014; Nijboer, van de Port, et al., 2013), leaving patients with neglect more dependent on their environment than stroke patients without neglect (Buxbaum et al., 2004; Nijboer, van de Port, et al., 2013). As a result, proper diagnosis of neglect is regarded as highly important for goal setting in rehabilitation.

In general, neuropsychological paper-and-pencil tasks, such as cancellation or bisection tasks, are used in the diagnosis of neglect. Some patients, however, do not show neglect on paper-and-pencil tasks, but do during activities in daily life (ADL), such as washing or eating, especially in the chronic phase post-stroke onset when patients have learned compensatory strategies (Azouvi, 2017; Bonato, 2015; Huisman et al., 2013; Ten Brink et al., 2013). There are several explanations for this discrepancy. First, neglect is a heterogeneous syndrome, varying in sensory modality (e.g., visual, auditory, and tactile neglect), distance (e.g., personal, peripersonal, and extrapersonal neglect), and frame of reference (e.g., egocentric or allocentric neglect; Corbetta 2014; Van der Stoep et al. 2013). Paper-and-pencil tasks are often designed to objectify *visual* neglect in *peripersonal* space. Second, in dynamic daily life situations, relevant stimuli have to be detected within a continuously moving environment in which one is also moving. There is little time to attend to objects, as stimuli are on the retina for a short amount of time, and there is strong competition between objects that draw attention (attention is drawn strongly to moving distractors). Objects on the neglected side, therefore, receive less attention and will be missed (Corbetta et al., 2005; Rengachary, D'Avossa, Sapir, Shulman, & Corbetta, 2009). Finally, during paper-and-pencil tasks, patients can focus on one goal. When patients have to perform multiple operations simultaneously, such as walking, chatting, and looking, the attentional capacity is limited, and it is more likely that signs of neglect will be shown (Blini et al., 2016; Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; van Kessel, van Nes, Geurts, Brouwer, & Fasotti, 2013). To conclude, many factors are disregarded in standard paper-and-pencil tasks leading to a lack of sensitivity in the diagnosis of neglect.

In order to assess the presence of neglect and neglect severity in a more sensitive way, complementary tasks can be administered. One possibility is to observe neglect behaviour during ADL with a structured observation scale such as the Catherine Bergego Scale (CBS; Azouvi et al., 2003; Ten Brink et al., 2013). Alternatively, a multitask, such as the Mobility Assessment Course (MAC), can be administered. The design of the MAC is based on the visual search task of Verlander et al. (2000). During this task, participants have to perform a simple wayfinding task in a corridor while finding targets and reporting them. Due to higher cognitive (and motor) load, there is less room for using compensation strategies. Such a multitask might therefore assess the presence and genuine severity of neglect that patients might also demonstrate in real life. In the original study, the interrater reliability of the MAC was high (Verlander et al., 2000).

Aims of the current study were to assess the feasibility of the MAC in a rehabilitation setting and to evaluate the relation of the MAC with existing neglect tasks. First, the feasibility of administering the MAC in daily practice in a rehabilitation centre was studied by evaluating the percentage of stroke patients who could complete the MAC, the total time to complete the MAC, and the percentage of targets that were visible during task administration. Second, to determine whether the MAC can be assessed in different corridors, the performance of healthy control subjects and the degree of crowdedness were compared between two corridors. Finally, we evaluated to what extent performance on the MAC relates to performance on standard neuropsychological neglect tasks (cancellation and line bisection) as well as observations with the CBS. As there is currently not one gold standard for the assessment of neglect, the rationale for the comparisons with existing tasks was to study what potential differences exist in overall detection rates of patients with neglect.

Material and methods

Participants

We included patients who were admitted to inpatient rehabilitation in De Hoogstraat Rehabilitation centre. Patients with neglect were recruited via a larger randomized controlled trial (PAiR; Ten Brink, Visser-Meily, & Nijboer, 2015; #NTR3278; approved by the Medical Ethical Committee of the University Medical Centre Utrecht, #12-183/O). Patients without neglect were recruited via a neglect screening.

Inclusion criteria for the current study were: (a) clinically diagnosed symptomatic stroke (ischemic or intracerebral haemorrhagic lesion, confirmed with CT or MRI scans), first or recurrent; (b) 18-85 years of age; (c) sufficient communication and comprehension (assessed by a neuropsychologist); (d) physically and cognitively able to participate (assessed by a rehabilitation physician); and (e) unilateral lesion (to be able to recode the target sides as contralesional or ipsilesional). Finally, healthy controls with a comparable age distribution were recruited among relatives of the staff. Measurements took place at three locations, from May to November 2011, December 2013 to July 2015, and August 2015 to August 2016. All participants gave written informed consent. The experiment was performed in accordance with the Declaration of Helsinki.

Procedure and tasks

We reviewed the patient's medical record and captured demographic and clinical characteristics. All patients were screened for neglect (with a shape cancellation task, a line bisection task and the CBS) as usual care within the first two weeks after admission to the rehabilitation centre if their condition permitted testing (referred to as "Session 1"). This neglect screening took about 45 min. Approximately two weeks later, the MAC and shape cancellation were administered for research purposes within a 30-min session (referred to as "Session 2"). Additionally, neglect patients (recruited via the PAiR study) were also tested with the line bisection, and observations were again obtained with the CBS during Session 2 (Figure 4.1).

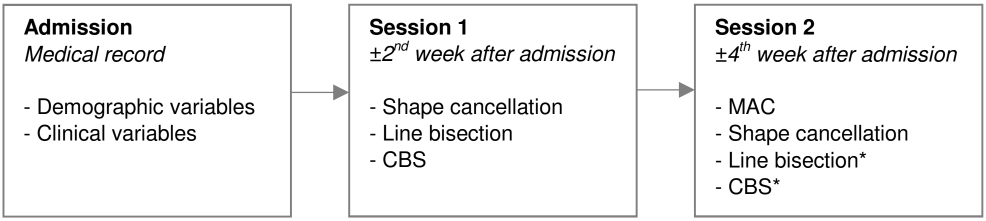


Figure 4.1 **Schematic overview of data collection per session. *These tasks were administered only in patients who participated in the randomized controlled trial.**

Medical record

Education level was assessed using seven categories of a Dutch classification system, according to Verhage, 1 being the lowest (less than primary school) and 7 being the highest (academic degree; Verhage 1964) These levels were converted into three categories: low (Verhage 1-4), average (Verhage 5), and high (Verhage 6-7).

Global cognitive functioning was screened with either the Mini-Mental State Examination (MMSE; Folstein et al., 1975) or the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Both tests globally assess cognitive functioning, including memory, visuospatial abilities, executive functions, attention, language, and orientation in time and place. Scores range from 0 (no items right) up to 30 (all items right). For the first half of included patients, MMSE scores were obtained rather than MoCA scores due to hospitals' protocol changes. We converted MMSE scores into MoCA scores to create a single, pooled MoCA score. We applied the following formula: MoCA = (1.124 x MMSE) – 8.165 (Solomon et al., 2014).

Communication skills were determined with the "Stichting Afasie Nederland" test (SAN; Deelman et al., 1981), an observation scale for language communication. Scores range from 1 (no communication through language possible) to 7 (speech and understanding of language are unimpaired).

Muscle strength was measured by the Motricity Index (Collin & Wade, 1990), a short 3-item task to assess the loss of strength in a limb. Scores range from 0 (no activity, paralysis) up to 33 (maximum normal muscle force) for each extremity. In the case of 99 points, one point is added to reach a total score of 100. The Motricity Index was assessed for both the upper and the lower extremity.

Independence in ADL was assessed using the Barthel Index (Collin et al., 1988), which measures the extent to which stroke patients can function independently in their ADL. Scores range from 0 (completely dependent) up to 20 (completely independent).

Mobility Assessment Course

The MAC was administered in two buildings, in three corridors (Figure 4.2). There was no reception or main entrance in the corridors, however, therapists, patients, and visitors could enter the corridors.

Along the corridors, 24 targets (yellow, 10 x 10 cm; Figure 4.3) were attached to the walls, 12 on each side. As in the study of Verlander et al. (2000), targets in Corridors 1 and 2 were obstructed from view until the participant approached the target. Active search was necessary for identification. This was obtained by positioning targets next to a protruding object, such as a painting or a door. In Corridor 3, the walls were flat.

Targets were located at three different heights (4 low: 40-85 cm, 4 mid-height: 85-125 cm, and 4 high: 125-165 cm). For patients who were seated in a wheelchair, targets were located at two heights (4 low: 40-85, and 8 mid-height: 85-125 cm). For each corridor, three conditions were used, in which the height of the targets was varied per target location. Conditions were randomized across participants. At every turn, an arrow was attached (black on a light yellow background, A4 size; Figure 4.3).

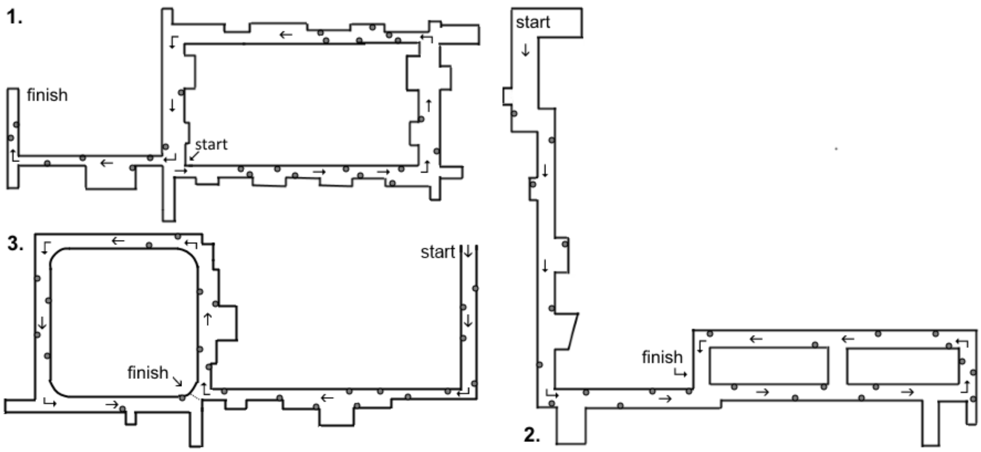


Figure 4.2 Map of the Mobility Assessment Course in the three corridors

Figure 4.3 Target (left) and arrow (right).

Participants were instructed to walk or drive independently at a leisurely pace, without stopping or turning back. Meanwhile, participants had to point out the targets (Figure 4.4). Sample targets were shown during the instructions. It was emphasized that there was no time limit, and finding all targets was the main goal. Because patients were required to actively move (i.e., no assistance was offered during assessment, unless potential precarious situations were to occur), the experimental setting can be considered multitasking.

The following components were scored: number of omissions (left and right separately), the number of collisions, the number of corrections when someone took the wrong direction, the task duration (in minutes), and the number of people, ranging from 1 (empty) to 4 (over five groups of people). When a target location was not visible during the task - for example, due to obstruction by a person or object - this target was not included in the computation of the total amount of omissions. The number of omissions was divided by the number of visible targets and was multiplied by the maximum amount of targets [e.g., (4 / 11) x 12]. The asymmetry score was computed as the absolute difference between the number of omissions on the left and the right.

Figure 4.4 Assessment of the MAC in a patient with neglect.

Shape cancellation task

The shape cancellation task consisted of 54 small targets, 52 large distractors, and 23 words and letters. Patients were instructed to cancel all targets and to tell the examiner when they had completed the task. No time limit was given. The threshold for neglect was based on the performance of 28 healthy individuals. The average omission difference score plus 3 *SD* was 1.05, resulting in a threshold of ≥2 (Van der Stoep et al., 2013).

Line bisection task

The line bisection task consisted of three horizontal lines (22° long and 0.2° thick), presented on the upper right, lower left, and in the horizontal and vertical centre of a computer screen. The amount of horizontal shift between lines was 15% of the line length. The stimulus presentation was approximately 19° wide and 5.7° high. Patients were asked to mark the subjective midpoint. For each line, the threshold for neglect was based on the performance of 28 healthy subjects. The normal range, based on the average deviation plus 3 *SD*, was –0.77 to 0.81°, –0.85 to 0.48° and –0.89 to 0.42° for the three lines respectively (Van der Stoep et al., 2013). A deviation above threshold (i.e., outside normal range) on ≥2 lines was used as a threshold for neglect.

Catherine Bergego Scale

The CBS is an observation scale for neglect in ADL (Azouvi et al., 2003; Ten Brink et al., 2013). It assesses performance in personal (body parts, body surface), peripersonal (within reaching distance), and extrapersonal space (beyond reaching distance), as well as in perceptual, representational, and motor domains. For 10 items, presence and severity of neglect were scored by the nurse, resulting in a total score of 0 (never/no neglect) to 30 (always/severe neglect). Nurses were instructed to score only behaviour due to neglect and not due to other deficits (e.g., motor and/or sensory deficits). A score of ≥6 was used as a threshold for neglect (Ten Brink et al., 2013).

Statistical analyses

Demographic and clinical characteristics

Descriptive data on age, sex, and level of education were provided for the stroke patients and healthy control subjects. A Mann-Whitney test and Chi-Square test was used to compare demographic variables between the two groups. Descriptive data on clinical characteristics (i.e., time post-stroke onset, stroke history, stroke type, lesion side, MoCA, SAN, Barthel Index, and Motricity Index arm and leg) were provided for the stroke patients.

Feasibility

We aimed to evaluate whether the MAC can be used as a tool within the neuropsychological assessment. Therefore, we computed the percentage of patients who were able to perform the MAC and the total time patients needed to complete the MAC. Neuropsychological tasks usually do not take more than 5 to 10 min on average. In addition, the percentage of targets that were visible (i.e., targets that were not obstructed by persons or objects) during task administrations of all subjects was computed, to determine whether administering the MAC is feasible in daily practice in a rehabilitation centre.

In order to determine whether scores can be compared among different corridors, the number of omissions (total, left, and right), the asymmetry score, and the degree of crowdedness were compared between Corridors 1 and 3 with a Mann-Whitney test, with data of healthy control subjects. Not enough data was available to statistically compare performance in Corridor 2.

Relation with existing neglect tasks

Patients were grouped based on the shape cancellation and line bisection task. Patients who showed neglect during Sessions 1 and 2 on either the shape cancellation or line bisection task were referred to the neglect group. Patients with neglect on either the shape cancellation or the line bisection task during Session 1, but not during Session 2, were referred to the recovered group. Patients who did not show neglect during Session 1 were referred to the no neglect group. Differences in performance at the MAC (the total, contralesional, and ipsilesional number of omissions, asymmetry score, collisions, and corrections for direction) between patients with neglect, recovered, and without neglect as measured with neuropsychological tasks were assessed with a Mann-Whitney test.

The threshold for neglect as measured with the MAC was based on the average asymmetry score of healthy control subjects +2.5 *SD*. Percentages of patients with and without neglect as measured with the MAC were provided, split for patients with and without neglect based on three different tasks (shape cancellation, line bisection, and CBS).

For patients with neglect at any of the tasks (shape cancellation, line bisection, or CBS) during Session 1, Spearman correlations between the MAC scores and performance at the shape cancellation, line bisection, and CBS (all measured during Session 2) were computed. An r of .1 was considered a small, .3 a moderate, and .5 a large correlation (Field, 2013).

For all statistical comparisons and the correlations, the level of significance was set at $p = .05$.

Results

Demographic and clinical characteristics

In total, 113 stroke patients and 47 healthy control subjects were included (Table 4.1). The age of the two groups was comparable, $U = 2139$, $p = .053$. The distribution of sex differed between groups, with fewer men in the control group than in the patient group, $\chi^2(1) = 12.10$, $p = .001$. Furthermore, the level of education was higher in the control group than in the patient group, $\chi^2(2) = 18.53$, $p < .001$.

Table 4.1 Demographic and clinical characteristics, percentages, medians and interquartile ranges

Outcome	Patients			Controls		
	n	*Mdn*	*IQR*	*n*	*Mdn*	IQR
Age, years	113	59.67	13.70	47	56.99	13.64
Sex, % male	113	71.7		47	42.6	
Level of education	109			47		
% Low		25.7			6.4	
% Average		36.7			19.1	
% High		37.6			74.5	
Time post-stroke onset, days	113	37	25.5			
Stroke history, % first	90	84.4				
Stroke type	88					
% Ischemic		77.3				
% Intracerebral haemorrhage		19.3				
% Subarachnoid haemorrhage		3.4				
Lesion side, % left	113	41.6				
MoCA (0-30)	79	22	7.43			
SAN (1-7)	89	6	2			
Barthel Index (0-20)	100	10	10			
Motricity Index arm (0-100)	88	70.5	100			
Motricity Index leg (0-100)	90	75	72			

Abbreviations: MoCA, Montreal Cognitive Assessment; SAN, Stichting Afasie Nederland.

We tested whether differences existed regarding the number of omissions, asymmetry score, collisions, and corrections based on sex (using a Mann-Whitney test) or on the level of education (using a Kruskal-Wallis non-parametric ANOVA). Comparisons were made separately for the stroke patients and healthy control subjects. No significant differences were observed on any of the comparisons regarding sex within the stroke patients (all $p \geq .139$) or healthy controls (all $p \geq .245$), or regarding the level of education within the stroke patients (all $p \geq .075$) or healthy controls (all $p \geq .305$).

Feasibility

Of 113 patients, 112 patients (99.1%) could complete the task. Patients were able to move independently along the corridor. One patient (with neglect) walked with the aid of a stick, but he could not finish walking the complete route because after a few minutes he was unable to support his weight. Subsequently, we adjusted the protocol such that patients who appeared to lack sufficient strength or stamina to walk the complete route, completed the task in their wheelchair instead. The number of omissions for this patient was included in the study, corrected for the number of targets that were presented until the task was aborted.

The duration of the task ranged from 2.22 to 9.37 min, with a median duration of 4.17 min.

In Corridors 1, 2, and 3, all targets were visible during 88.5%, 88.6%, and 93.3% of task assessments, respectively. In assessments in which not all targets were visible, only 1 or 2 targets were obstructed (by a person or an object).

The total number of omissions, $U = 68.5$, $p < .001$, left, $U = 94.5$, $p < .001$, and the number of right omissions, $U = 121.5$, $p = .003$, of healthy control subjects were higher in Corridor 1 than in Corridor 3 (Table 4.2). It is important to note that in Corridors 1 and 2 targets were placed next to objects that protruded, which was not the case in Corridor 3. The objects in Corridors 1 and 2 were therefore only visible from a short distance, whereas targets in Corridor 3 could be seen from further away. The asymmetry score did not differ between corridors, $U = 169.5$, $p = .077$. Furthermore, the level of crowdedness was comparable, $U = 223$, $p = .848$.

Table 4.2 MAC scores, medians and interquartile ranges of healthy control subjects, split per corridor

Outcome	Corridor 1	Corridor 2	Corridor 3
n	20	3	24
MAC omissions			
Total (0-24)	2.0 (4.0)	2.1 (0)	0.5 (1.0)
Left (0-12)	1.0 (1.8)	2.0 (0)	0 (0)
Right (0-12)	1.5 (1.8)	1.0 (0)	0 (1.0)
Asymmetry score	1.0 (1.8)	1.0 (0)	0 (1.0)
Crowdedness (1-4)	2 (1)	2 (0)	2 (2)

Abbreviation: MAC, Mobility Assessment Course.

Relation with existing neglect tasks

Of all stroke patients, 37 patients showed neglect during the first and second session, 10 patients showed neglect during the first session and not during the second session, and 60 patients did not show neglect (Table 4.3).

The neglect patients obtained a higher number of total and contralesional omissions, and a higher asymmetry score compared to patients without neglect (total: $U = 296.5$, $p < .001$; contralesional: $U = 323$, $p < .001$; asymmetry: $U = 445.5$, $p < .001$), and compared to the recovered patients (total: $U = 110$, $p = .050$; contralesional: $U = 102.5$, $p = .031$; asymmetry: $U = 91$, $p = .014$). No differences were seen regarding the number of ipsilesional omissions between patients with neglect and without neglect ($U = 959.5$, $p = .229$) and between patients with neglect and the recovered patients ($U = 174$, $p = .763$). The recovered patients did not differ from the non-neglect patients for any of the omission scores (total: $U = 199$, $p = .086$; contralesional: $U = 190$, $p = .057$; ipsilesional: $U = 269$, $p = .573$; asymmetry: $U = 226$, $p = .197$).

Neglect patients collided more than did patients without neglect, $U = 841$, $p < .001$, but not more than the recovered patients, $U = 135$, $p = .069$. No difference was seen between the recovered patients and patients without neglect, $U = 290$, $p = .561$. Of all neglect patients, 27% bumped at least once, whereas only 3.3% of the non-neglect patients and 0% of the recovered patients bumped. As there were only little collisions, this measure

Table 4.3 MAC scores, medians and interquartile ranges of patients with and without neglect

Outcome	Neglect	Recovered	No neglect
n	37	10	60
Lesion side left/right	2/35	5/5	35/25
Walking/wheelchair	13/24	4/6	40/20
MAC omissions			
Total (0-24)	8.0 (5.0)	4.5 (8.0)	2.0 (3.0)
Contralesional (0-12)	4.5 (8.0)	4.0 (7.0)	1.0 (2.0)
Ipsilesional (0-12)	1.0 (3.0)	1.0 (2.0)	0.0 (2.0)
Asymmetry	7.0 (7.5)	3.5 (5.3)	1.0 (1.8)
MAC collisions	0 (1)	0 (0)	0 (0)
MAC corrections	0 (1)	0 (0)	0 (0)

Abbreviation: MAC, Mobility Assessment Course. Note. Neglect = patients with neglect during Session 1 and Session 2. Recovered = patients with neglect during Session 1, and without neglect during Session 2. No neglect = patients without neglect during Session 1.

provides no additional information regarding neglect (see also Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008; Verlander et al., 2000).

Finally, patients with neglect went in the wrong direction more often than did patients without neglect, U = 818, p = .004, but not more often than did the recovered patients, U = 126, p = .067. Patients without neglect did not differ from recovered patients, U = 284, p = .658. Of patients with neglect, 40.5% had to be corrected at least once, whereas 15% of the non-neglect patients and 10% of the recovered patients had to be corrected.

The average asymmetry score of healthy control subjects was 0.75 (SD = 0.81). Based on this, the threshold for neglect was an asymmetry score of 2.78. Of patients with neglect on the cancellation task at both sessions, 82.8% showed neglect on the MAC (Table 4.4). In the recovered group this was 66.7%, whereas 9.5% of patients without neglect as measured with the shape cancellation task showed neglect on the MAC. When patients were grouped based on the line bisection, 81% of patients with neglect during both sessions showed neglect on the MAC. In the recovered group, 60% showed neglect as measured with the MAC. Of patients without neglect on the line bisection, 18.6% showed neglect on the MAC. Within the group of patients with neglect as measured with the CBS during both sessions, 70.7% showed neglect on the MAC as well, whereas this was 33.3% in the recovered group. Only 4% of patients without neglect on the CBS, did show neglect on the MAC.

The number of total omissions, contralesional omissions, and the asymmetry score at the MAC showed large positive correlations with the shape cancellation and moderate positive correlations with the line bisection and CBS total score (Table 4.5). The CBS items “grooming”, “looking toward one side”, “forgetting part of body”, “orienting of attention”, and “colliding” showed a moderate positive relation with the total number of omissions, contralesional omissions, and asymmetry score obtained with the MAC. The items “way finding” and “finding personal belongings” showed a moderate positive relation with the total number of omissions and the contralesional omissions at the MAC. The items “adjusting clothes”, “food on plate”, and “mouth cleaning” were not related to performance at the MAC.

Table 4.4 Percentages of patients with neglect during the MAC, split for patients with and without neglect based on three different tasks

	Shape cancellation (*n* = 112)			Line bisection (*n* = 90)			CBS (*n* = 103)		
	Neglect	Recovered	No neglect	Neglect	Recovered	No neglect	Neglect	Recovered	No neglect
N	29	9	74	21	10	59	41	12	50
MAC neglect									
% Neglect	82.8	66.7	9.5	81	60	18.6	70.7	33.3	4
% No neglect	17.2	33.3	90.5	19	40	81.4	29.3	66.7	96

Abbreviations: CBS, Catherine Bergego Scale; MAC, Mobility Assessment Course.

Note. Neglect = patients with neglect during Session 1 and Session 2. Recovered = patients with neglect during Session 1, and without neglect during Session 2. No neglect = patients without neglect during Session 1.

Table 4.5 Spearman correlations between the MAC, shape cancellation, line bisection, and CBS

Outcome	MAC omissions			
	Total	Contralesional	Ipsilesional	Asymmetry
Shape cancellation, asymmetry (*n* = 69)	.53**	.52**	.04	.56**
Line bisection, deviation (*n* = 57)	.38**	.39*	.06	.39**
CBS total score (*n* = 54)	.42**	.45**	–.01	.48**
1. Grooming (*n* = 50)	.28*	.32*	–.09	.35*
2. Adjusting clothes (*n* = 41)	.15	.14	–.01	.25
3. Food on plate (*n* = 49)	.07	.13	–.15	.22
4. Mouth cleaning (*n* = 48)	.18	.21	–.02	.27
5. Looking towards one side (*n* = 47)	.39**	.38**	.18	.33*
6. Forgetting part of body (*n* = 45)	.31*	.34*	.03	.30*
7. Orienting of attention (*n* = 49)	.34*	.38**	–.03	.41**
8. Colliding (*n* = 51)	.49**	.51**	.12	.46**
9. Way finding (*n* = 47)	.33*	.30*	.17	.23
10. Finding personal belongings (*n* = 48)	.35*	.33*	.16	.23

Abbreviations: CBS, Catherine Bergego Scale; MAC, Mobility Assessment Course.
Note. $^*p \leq .05$, $^{**}p \leq .01$.

Discussion

Aims of the current study were to determine the feasibility of the MAC, a task that could be used as an ecologically valid multitask in the assessment of neglect, and its relation to existing neglect tasks. Administering the MAC as part of a neuropsychological assessment seems feasible, as all patients, with the exception of one, (99.1%) who were able to perform standard neuropsychological assessment could also complete the MAC. In addition, the median task duration was only 4.17 min, which is comparable to the administration time of a standard neuropsychological paper-and-pencil task. Furthermore, depending on the corridor where the MAC took place, in 6.7 to 14.5% of all assessments a maximum of two targets was obstructed. This indicates that setting up a route with targets that are visible is possible in the corridor of a rehabilitation centre.

Patients with neglect at paper-and-pencil tasks had more omissions during the MAC than did patients without neglect, indicating that there is agreement between these tasks. Nevertheless, 9.5 to 18.6% of patients *without* neglect as assessed with neuropsychological assessment showed neglect as measured with the MAC. This strengthens the view that clinical diagnosis of neglect requires more than a significant difference on one test, preferably across tests of varying dynamics and complexity. For some patients, the reverse pattern was seen: 17.2 to 19% showed neglect as measured with neuropsychological assessment, but *not* at the MAC. The variation in percentages of patients with neglect across tasks could relate to the heterogeneity of the neglect syndrome. One possible explanation for these seemingly contradictory findings might lie in the level of arousal needed to perform those different tasks. A subset of patients with neglect is known to have severe problems in maintaining arousal during tasks. It might be that for some patients the MAC as a multitask - encompassing multisensory stimulation, for example Tinga et al. (2015) - maintains their level of arousal more than do the neuropsychological paper-and-pencil neglect tasks. In other patients, however, the lateralized attention deficit as the core of the neglect syndrome may appear aggravated due to the complex and dynamic nature of the tasks. To exactly pinpoint the underlying mechanisms in (individual) patients with neglect is still difficult. With respect to the MAC and its relation to other neglect tasks, the use of the MAC would at this stage be a supplementary one.

Additionally, the results of the 'recovered' group (i.e., patients who only showed neglect during the first session but not during the second session) are remarkable, as 60 to 66.7% of patients in this group showed neglect as measured with the MAC, whereas these patients did not show neglect on the second session with the neuropsychological neglect tasks. These results fit the clinical observations that neuropsychological assessment is not always sensitive enough to detect neglect, especially when there is no time limit, when stimuli are static, and when the attentional load is low (Azouvi, 2017; Huisman et al., 2013; Ten Brink et al., 2013). The MAC may detect neglect in 'recovered' patients due to its complex and dynamic nature in which the lateralized attention deficit could manifest. There is ample evidence that 'recovered' patients can show large attentional asymmetries while dual-tasking (e.g., Bartolomeo, 1997; Blini et al., 2016; Bonato, Priftis, Umiltà, & Zorzi, 2013; Bonato, 2015; van Kessel et al., 2013), suggesting that at least some of the patients within this group are most likely not actually recovered. The MAC appears to be an ecologically valid, dynamic multitask that is quite easy to implement in *clinical practice*.

Severity of neglect as measured with the MAC related to neglect severity as measured with standard neglect tasks. Specifically, a strong positive relation was seen between asymmetry scores obtained at the MAC and asymmetry scores obtained at the shape cancellation task. Visual search is the key aspect in both tasks, and eye movements are most probably the common feature (head movements to a somewhat lower extent) in both tasks. The spatial bias is in both tasks the most important outcome measure. Such a strong positive relation is therefore not surprising. There is one aspect that might be measured with the MAC that cannot be easily measured with cancellation tasks, and that is region specificity of neglect (but see also below). As double dissociations exist between neglect in peripersonal and extrapersonal space, this could explain why some patients showed neglect on one task and not on the other (Berti & Frassinetti, 2000; Van der Stoep et al., 2013).

A moderate positive relation was found between the performance on the MAC and the magnitude of displacement of the bisection mark. Given the differences in nature of both tasks, this is also an interesting finding. At the line bisection task patients have to estimate the middle of a line. A lack of attention to one side of the line results in a deviation of the estimated middle toward the opposite side. Contrary to the MAC and the cancellation task, the line bisection task depends primarily on the perceptual estimation of a single stimulus without the competition of other stimuli (Ferber & Karnath, 2001). Perceptual estimations are also components of the MAC, albeit to a much lesser extent: such deviations during an ecologically valid task in which observations are the secondary most important outcome measure, are much more difficult to scrutinize. When perceptual estimations in neglect are the focus of research or assessment, one could make better use of a more fine-grained measure.

Another complementary tool for assessment of neglect in ADL is the CBS. In prior studies, the relation between the CBS and paper-and-pencil tasks was assessed, and the CBS detected about 10% of patients who did not show neglect at standard neuropsychological assessment, and vice versa (Azouvi et al., 2003; Ten Brink et al., 2013). In the current study, more patients were diagnosed with neglect based on the CBS (40%) compared to neuropsychological assessment (23 to 26%). In addition, only 4% of patients who did not show neglect based on the CBS were diagnosed with neglect based on their performance on the MAC. This might suggest that adding the CBS to a standard neglect battery would suffice. However, observed neglect behaviour in ADL, as measured with the CBS, showed only a moderate positive relation with performance at the MAC. Similarities with the MAC are that the CBS also includes the dynamic character of daily life, and observations can be made while patients have to attend to different regions of space (Nijboer, Ten Brink, Kouwenhoven, et al., 2014). However, there are also important differences between the MAC and CBS that would warrant the use of both instruments. First, the CBS lacks explicit multitasking and measures of divided attention. In addition, a larger variety of situations and constructs are included in the CBS compared to the MAC (Goedert et al., 2012). There were significantly positive relations between performance on the MAC and all CBS items, except “adjusting clothes”, “food on plate”, and “mouth cleaning”. Given the dynamic nature of the MAC (i.e., continuous movements) in combination with the wayfinding and object-finding elements, it is very likely that both peripersonal and extrapersonal neglect could be detected. As people move forward through a corridor, elements that appear in extrapersonal space slowly come nearer. Observations are in the current form of the MAC the only way to ‘measure’ when and where elements are noticed and access awareness. This is not a very neat measure, however, to differentiate between region-specific types of neglect. Notwithstanding its imprecise indication of attended elements in different regions of space, the MAC in its current form is likely to give extra observational information on attention processing in different regions of space. When one wants to have more precise measures of access awareness of objects in different regions of space, virtual reality tasks can be used in which eye tracking can give very detailed information on the when and where of object awareness.

Moving independently and obtaining a good spatial orientation are important goals in clinical rehabilitation, as they are important for participation. Nevertheless, these aspects are rarely considered in the diagnosis of neglect. The MAC provides a semi-structured framework to assess neglect. In general, healthy control subjects perform well, and the difference in performance between corridors is small (asymmetry scores of 0.96 and 0.55). In addition to quantitative information, observations can be made during the MAC. More specifically: the position of the head or the occurrence of head movements, the position in the corridor and the occurrence of collisions can be observed. The task can also be used to practice visual scanning or to provide insight to the patient. With the latter aim, the task can be assessed multiple times, for example in reversed order so that the patient becomes aware of the number of targets that were missed during the first assessment. It should be emphasized that, as with neuropsychological assessment, the complete profile of performances at different tasks is important for the diagnosis of neglect, in combination with qualitative observations. For example, a patient with left-sided neglect could miss targets on the right side, due to overcompensation or by remaining at the right side of the corridor, and observations during the MAC are necessary for adequate interpretation of the outcomes.

Several other tasks are developed to assess neglect in a dynamic or ecologically valid manner. Detection tasks in which reaction times of responses are measured, combined with other tasks (such as discrimination tasks), are more demanding and more sensitive to the lateralized attentional deficit compared to static tasks (Bonato et al., 2010; Russell, Malhotra, & Husain, 2004). Such dual-tasks, especially in a daily setting or as a daily activity to enlarge the external validity, add to the current diagnostics (Marshall, Grinnell, Heisel, Newall, & Hunt, 1997; van Kessel et al., 2013).

Limitations

One limitation is that tasks in which a daily life setting is used can never be completely standardized across settings. First, corridor features, for example, the length of the route, the number of turns, the color of the walls, and the possibility to place targets behind protruding parts differ between institutions. Second, other activities that take place in the corridor cannot be controlled for, and thus the crowdedness can vary per assessment and is likely to have an impact on the overall performance of patients. Therefore, it is crucial to explore each corridor and investigate performance in a representative group of healthy control subjects, as we did in the current study. Still, one does not have control over activities in a corridor during assessment. Neglect assessment using the MAC in a somewhat secluded corridor might be an option in some, but not all institutions. For better control of activities in such daily life settings, virtual reality simulations may be used in the future, allowing patients to perform a cognitive multitask while interacting with the fully controlled environment.

In addition, when tasks are assessed in daily life situations in which active movement of the patient is required, which is the case during the MAC and the CBS, effects of motor impairments could affect performance. For example, loss of strength in one arm could lead to an asymmetric wheelchair driving pattern during the MAC or adjusting clothes as one of the items of the CBS. Although the staff was trained to score deficient behaviour with both the CBS and the MAC, the interaction between neglect and motor deficits is a complex one and observations leave room for different interpretations. In our study, only one neuropsychologist (MAC) or one nurse (CBS) observed each patient. An improvement might be to always have two persons observe and rate patient behaviour, yet this might be difficult to accomplish in a clinical setting.

Potentially, other disorders of visual perception, such as scotoma and hemianopia, might also result in omissions at the MAC (Verlander et al., 2000). Observations of the neuropsychologists during the MAC are therefore of utmost importance, as the behavioural consequences, also as the result of awareness of the disorder and the ability to (spontaneously) compensate, of hemianopia versus neglect are quite substantial, especially in the subacute phase post-stroke onset. In addition, it is important to always screen for scotoma and hemianopia, either with neurological and/or behavioural tasks and/or with MRI scans.

Conclusions

The MAC is a visual search - multitask during which quantitative and qualitative data can be collected. Due to higher cognitive and motor load and the dynamic character of the task, there is less room for using compensation strategies. A structured observation, which can be obtained during the MAC, provides relevant information in addition to quantitative data. Administering the MAC seems feasible in stroke patients in a rehabilitation setting. There is a moderate to high agreement between the MAC and existing paper-and-pencil tasks for neglect. However, some stroke patients perform normally on paper-and-pencil tasks, but they show neglect as measured with the MAC, and vice versa. The variation in percentages of patients with neglect across tasks could relate to the heterogeneity of the neglect syndrome. To conclude, the MAC could be administered along with paper-and-pencil tasks to assess the existence of neglect and neglect severity in a dynamic way.

Acknowledgements

This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN, and the "Revalidatiefonds" under grant R2012134 to TCWN and JMAVM. We would like to thank Merel Pieters, Marit Dorresteijn, Roemi Wikarta, Sanne Loosschilder, Inge Meeuwissen and Irene Bonthond for their help in collecting the data.

Chapter 5

You never know where you are going until you know where you have been: Disorganized search after stroke

Ten Brink, A. F., Van der Stigchel, S., Visser-Meily, J. M. A., Nijboer, T. C. W. (2016). You never know where you are going until you know where you have been: disorganized search after stroke. *Journal of Neuropsychology, 10*(2), 256-275.

Abstract

Disorders in spatial exploration can be expressed in a disorganized fashion of target cancellation. There is debate regarding whether disorganized search is related to stroke in general, to right brain damage, or to unilateral spatial neglect (USN) in particular. In this study, 280 stroke patients and 37 healthy control subjects performed a computerized shape cancellation test. We investigated the number of perseverations and several outcome measures regarding disorganized search: consistency of search direction (best *r*), distance between consecutive cancelled targets and intersections with paths between previous cancelled targets. We compared performance between patients with left and right brain damage (L, R) and with and without USN (USN+, USN-), resulting in four subgroups: LUSN, RUSN, LUSN+, and RUSN+. Higher numbers of intersections were found for the left brain- and right brain-damaged patients with USN and for the right brain-damaged patients without USN, compared to healthy control subjects. Furthermore, right brain-damaged patients with USN showed a higher number of intersections compared to right brain-damaged patients without USN and compared to left brain-damaged patients with USN. To conclude, disorganized search was most strongly related to the neglect syndrome, and patients with more severe USN were even more impaired.

Introduction

Cancellation tests are widely used to detect unilateral spatial neglect (USN) in stroke patients, as they are the most sensitive among pencil-and-paper tests (Halligan, Marshall, & Wade, 1989; Machner et al., 2012). In cancellation tests, participants have to mark target shapes that are interspersed with distractors. The number of unmarked targets is a measure of spatial inattention, and a difference of at least two or three omissions between both sides of the stimulus field is generally used as an indication for USN (Mark et al., 2004; Tant, Kuks, Kooijman, Cornelissen, & Brouwer, 2002; Van der Stoep et al., 2013; Wilson, Cockburn, & Halligan, 1987). Thanks to digitalization of neuropsychological tests, more information can be gathered from a single test session, and multiple aspects can be analysed. One of them is the organization of search.

Healthy participants typically show organized search strategies when performing a cancellation test. They tend to use a structured, symmetrical pattern, make few errors, and recheck their work (Huang & Wang, 2008; Rabuffetti et al., 2012; Samuelsson, Hjelmquist, Jensen, & Blomstrand, 2002; Warren, Moore, & Vogtle, 2008). Stroke patients show less organized search patterns than healthy participants, either during visual search tests (Chédru, Leblanc, & Lhermitte, 1973) or cancellation tests (Chatterjee, Mennemeier, & Heilman, 1992). Several attempts have been made to investigate whether, and to what extent, search organization is altered in stroke patients in general, or in stroke patients with either right brain damage or USN in particular (Donnelly et al., 1999; Mark et al., 2004; Potter et al., 2000; Rabuffetti et al., 2012; Samuelsson et al., 2002; Weintraub & Mesulam, 1988; Woods & Mark, 2007).

Measures of search organization include consistency, distance and intersections. The *consistency* of the overall search pattern indicates whether one is searching in the same direction during the whole test, for example in a columnar fashion or row after row. The average *distance* between consecutive cancelled targets is based on the rationale that cancelling targets in close proximity would reflect efficient search, whereas cancelling distant targets reflects inefficient search. Finally, the number of *intersections* indicates the amount of crossings with paths between previously cancelled targets. More intersections would reflect less organized search.

There are conflicting results regarding search organization in patients with left and right brain damage or with and without USN. For example, it was found that patients with right brain damage searched in more directions (thus less consistent) compared to patients with left brain damage (Weintraub & Mesulam, 1988). Studies relating disorganized search to USN have only included right brain-damaged patients, because USN is more severe and persisting in patients with damage to the right hemisphere (Stone et al., 1993). Patients with USN searched more often from right to left than healthy control subjects (Donnelly et al., 1999; Rabuffetti et al., 2012). However, this does not imply *disorganized* search. In a verbal visual scanning test, right brain-damaged patients with USN read shorter sequences of symbols and made more shifts between scanning by column, by row, and diagonally, compared to right brain-damaged patients without USN, which indicates less consistent search (Samuelsson et al., 2002). However, Mark et al. (2004) saw no relation between overall search direction and USN severity. Additionally, no difference in *distance* between consecutive cancelled targets was observed between patients with and without USN (Mark et al., 2004; Rabuffetti et al., 2012). In one study, right brain-damaged patients with USN showed a higher number of *intersections* with paths between previous cancelled targets compared to right and left brain-damaged patients without USN (Rabuffetti et al., 2012), although no relation between the number of *intersections* and USN severity was found in another (Mark et al., 2004).

Comparisons between stroke patients and healthy control subjects in general (Woods & Mark, 2007), provide no information regarding the role of lesion side or USN in disorganized search. By including solely right brain-damaged patients, valuable information is missed, because presumably differences exist between left brain- and right brain-damaged patients regarding search organization (Weintraub & Mesulam, 1988). Furthermore, previous studies included small samples of patients (Mark et al., 2004; Samuelsson et al., 2002; Weintraub & Mesulam, 1988), used a limited number of targets (Donnelly et al., 1999), used non-computerized observations (Mark et al., 2004; Samuelsson et al., 2002; Weintraub & Mesulam, 1988), or looked at a restricted number of measures (Potter et al., 2000; Weintraub & Mesulam, 1988). In conclusion, there is no consensus yet whether right brain damage, USN, or both are related to disorganized search, and what outcome measure specifies organizational problems in stroke patients the best.

In this study, a computerized version of a shape cancellation test was used, which allowed calculating several standardized measures for search organization in a large sample of participants. Our aim was to investigate whether the number of perseverations and spatial organization measures (i.e., *consistency* of search direction, *distance*, and *intersections*) were related to stroke in general, right brain damage, or USN. First, we compared stroke patients with left or right brain damage and with or without USN versus healthy control subjects. Second, we compared the left with the right brain-damaged patients, within the USN subgroups. Finally, we compared patients with USN versus patients without USN within the left brain- and right brain-damaged patient subgroups.

Methods

Participants

Participants consisted of stroke patients who were admitted for inpatient rehabilitation from November 2011 to June 2014 in De Hoogstraat Rehabilitation centre. We screened patients according to the following inclusion criteria: (1) clinical diagnosed symptomatic stroke, first or recurrent, verified by magnetic resonance imaging (MRI) and/or computed tomography (CT) data; (2) no severe deficits in communication and/or understanding; (3) normal or corrected to normal visual acuity; (4) and the ability to perform the digitalized shape cancellation test (i.e., able to respond using a computer mouse and understand instructions). We excluded patients with bilateral damage. Patients were also tested with a standard neuropsychological screening, encompassing all cognitive domains. None of the patients had visual agnosia. There was no documentation of ataxia. We did not systematically assess visual field defects and (visual) extinction for this study. Patients with such deficits were included and no further distinction was made. Additionally, we included 37 healthy controls among relatives of the staff, and they were given reimbursement of expenses. The research and consent procedures were in accordance with the standards of the Declaration of Helsinki.

We reviewed the patient's medical record and captured the following admission to rehabilitation data: sex, age, lesion side, time post-stroke in days, global cognitive functioning score (Mini-Mental State Examination, MMSE; Folstein et al., 1975), level of independence during ADL (Barthel Index, BI; Collin et al., 1988), strength in the arm and leg (Motricity Index, MI; Collin & Wade, 1990), and the presence of language communication deficits (SAN, "Stichting Afasie Nederland" score).

Procedure and tests

All patients were screened for USN using a shape cancellation and line bisection test, as usual care within the first 2 weeks after admission to the rehabilitation centre. USN is a heterogeneous disorder and several processes are involved, which can be measured with different tests (Ferber & Karnath, 2001). We therefore determined the presence of USN first based on results of the shape cancellation test and then again based on results of the line bisection test. Furthermore, the latter test was not directly related to the search organizational measures. The order of the tests was randomized across participants. Participants were seated in front of a monitor at 120 cm. Participants had to use a computer mouse to click at stimuli on the screen.

Shape cancellation test

The shape cancellation test consisted of 54 small targets (0.6° × 0.6°), 52 large distractors, and 23 words and letters (widths ranging from 0.95° to 2.1° and heights ranging from 0.45° to 0.95°). The stimulus presentation was approximately 18.5° wide and 11° high. Participants had to click all targets and tell the examiner when they completed the test. No time limit was given. After each mouse click, a small circle appeared at the clicked location and remained on screen.

Patients with a difference score of two or more omissions between the two sides of the screen were assigned to either the left brain-damaged (LUSN+) or right brain-damaged (RUSN+) USN group. The other patients were assigned to the left brain-damaged (LUSN−) or right brain-damaged (RUSN−) group without USN.

Line bisection test

Three horizontal lines (22° long and 0.2° thick) were presented upper right, lower left, and in the horizontal and vertical centre of the screen. The amount of horizontal shift between lines was 15% of the line length. The stimulus presentation was approximately 19° wide and 5.7° high. Participants were asked to click on the subjective mid-point. The three lines were presented four times in a row, after which for each line the average deviation from the mid-point was calculated. The cut-off scores per line were defined as the mean deviation plus 3 *SD* of performance of 28 healthy participants (Van der Stoep et al., 2013).

Patients who showed an average deviation that was larger than the cut-off score at one of the three lines were reassigned to one of the USN+ subgroups. The other patients were reassigned to one of the USN− subgroups.

Outcome measures

The outcome measures of the shape cancellation test consisted of a time series including, for each click, the time of occurrence of the event and the horizontal and vertical screen coordinates of the clicked location. The original click coordinates within a radius of 50 pixels from the closest target were transformed into the target designated coordinates. Clicks at distractors or at random locations were not used for further analyses, because interpretation of these clicks was difficult. However, observations showed that these clicks were mostly due to either motor problems or inexperience with working with a computer mouse. Two target shapes in the centre were clicked by the examiner as an example and were also not used in analyses. We computed the following shape cancellation scores using all clicks on targets:

- *Omissions difference score*: The difference between the number of omissions between both sides of the screen.
- *Perseverations*: The number of non-consecutive perseverations, that is, number of targets clicked again after at least one other target clicked.

The following organizational measures were computed:

- *Consistency* of search direction: The Pearson correlation coefficient (r) from the linear regression of the x- or y-values of all marked locations relative to the order in which they were marked. The highest absolute correlation of these two was selected to represent the degree to which calculations were pursued orthogonally (Mark et al., 2004).
- *Distance*: The average of the Euclidian distances between consecutive clicks to targets.
- *Intersections*: The number of lines that crossed one or more paths between previous cancelled targets divided by the number of total possible intersections.

We computed the *organizational* measures (consistency, distance, and intersections) without the targets that were clicked as a consequence of rechecking, because the organizational measures can be negatively influenced by targets that are omitted in the first place but corrected afterwards (i.e., more intersections are made, the distance is larger, and

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the search direction is less consistent). We calculated the distances between the last five targets and removed each target and all consecutive targets from analyses in case the distance from the previous target was larger than the mean distance plus 2 *SD* of the whole test. The last four clicks to targets were still taken into account in calculating the omissions difference score and the number of perseverations. In computing the organizational measures, we included the perseverations in analyses.

Statistical analysis

The distribution of all variables was checked for normality by plotting histograms and computing *z*-scores for skewness and kurtosis. These calculations showed that the data were not normally distributed, so non-parametric tests were used.

The demographical characteristics (sex and age) were compared between the five groups (i.e., LUSN−, RUSN−, LUSN+, RUSN+, and the healthy control group) with a Kruskal-Wallis non-parametric ANOVA. Furthermore, the stroke characteristics and admission to rehabilitation data (days post-stroke, MMSE, BI, MI arm, MI leg, and SAN) were compared between the four stroke subgroups with a Kruskal-Wallis test. A post-hoc Mann-Whitney test was performed.

Regarding the different shape cancellation scores (omission difference score, perseverations, *consistency*, *distance*, and *intersections*), we compared each of the four stroke subgroups with the healthy control group, to explore whether the specific subgroups deviated from normal search. Hence, we performed four Mann-Whitney tests per outcome measure. A Bonferroni correction was applied to avoid a family wise error rate (adjusted level of significance for four tests per measure = .0125).

Second, we analysed whether the side of the lesion accounted for differences in search organization, by comparing LUSN− with RUSN− patients and LUSN+ with RUSN+ patients. Further, we examined the role of USN in disorganized search, by comparing LUSN− with LUSN+ patients and RUSN− with RUSN+ patients (adjusted level of significance for four tests per measure = .0125).

The omission difference score was used as an indication for neglect severity. For the patients with USN, correlations between the omission difference score and the four outcome measures (perseverations, *consistency*, *distance*, and *intersections*) were calculated using Spearman correlations. Spearman's rho was interpreted as small (> .1), moderate (> .3), large (> .5), or very large (> .7) (Dancey & Reidy, 2004).

Finally, patients were regrouped based on performance on the line bisection test. The differences of the LUSN− versus LUSN+ group and RUSN− versus RUSN+ group were examined using a Mann-Whitney test (adjusted level of significance for two tests per measure = .025).

Results

Demographic and stroke characteristics

In our sample of 280 patients, 26.5% of right and 13.5% of left brain-damaged patients showed USN (Table 5.1). The stroke subgroups and healthy control group were comparable regarding sex distribution, $\chi^2(4) = 3.95$, $p = .413$. However, the five groups differed regarding age, $\chi^2(4) = 18.88$, $p = .001$. All stroke subgroups had a higher age compared to the control group (LUSN−: $U = 1190$, $z = -4.03$, $p < .001$; RUSN−: $U = 1132$, $z = -3.93$, $p < .001$; LUSN+: $U = 179.5$, $z = -2.76$, $p = .006$; RUSN+: $U = 424$, $z = -3.09$, $p = .002$).[2] No differences existed between the four stroke subgroups ($U = 926$ to 6155, $z = -0.72$ to -0.11, all $p \geq .473$). The average ages in years were 44.05 ($SD = 20.10$) for the healthy control group, 59.14 ($SD = 10.87$) for the LUSN− group, 59.01 ($SD = 11.89$) for the RUSN− group, 59.50 ($SD = 14.23$) for the LUSN+ group, and 58.23 ($SD = 13.57$) for the RUSN+ group.

[2] To investigate whether the difference in age between the groups could account for potential results, we correlated age with the different measures within the healthy control group. None of the measures were significantly related with age (omissions: $r = .28$, $p = .095$; perseverations: $r = .06$, $p = .707$; best r: $r = -.08$, $p = .638$; distance: $r = .27$, $p = .101$), although a trend was found for a correlation between age and number of intersections ($r = .31$, $p = .064$).

Table 5.1 Mean scores and standard deviations of demographical and stroke characteristics among the five groups based on the shape cancellation test

Outcome	Controls (n = 37)	LUSN– (n = 115)	RUSN– (n = 108)	LUSN+ (n = 18)	RUSN+ (n = 39)
Sex (% male)	51.4%	64.4%	58.3%	44.4%	61.5%
Age	44.05 (20.10)	59.14 (10.87)	59.01 (11.89)	59.50 (14.23)	58.23 (13.57)
Days post-stroke	-	32.92 (36.72)	38.39 (58.46)	24.22 (14.44)	50.03 (40.40)
MMSE	-	24.92 (4.57)	27.24 (3.05)	24.14 (4.60)	25.67 (3.68)
BI	-	13.35 (5.50)	12.51 (5.21)	11.00 (5.24)	11.90 (4.78)
MI Arm	-	63.41 (39.00)	65.15 (36.71)	67.50 (39.94)	51.04 (40.22)
MI Leg	-	69.44 (34.65)	72.36 (30.39)	72.08 (35.42)	62.42 (36.48)
SAN	-	4.52 (2.06)	6.31 (1.04)	3.92 (1.94)	5.96 (1.29)
Omissions difference score	0.08 (0.71)	0.23 (0.43)	0.20 (0.41)	4.50 (5.78)	5.82 (5.27)
Line bisection (% USN+/USN–/not finished)	-	26/57/17	38/46/16	39/33/28	85/7.5/7.5
Line bisection (average deviation in deg.)	–0.15 (0.24)	–0.39 (0.91)	–0.10 (0.56)	–0.32 (0.88)	1.03 (1.72)

Abbreviations: BI, Barthel Index; MI, Motricity Index; MMSE, Mini-Mental State Examination; SAN, Stichting Afasie Nederland; USN, unilateral spatial neglect.

The stroke subgroups differed regarding the number of days post-stroke onset, $\chi^2(3) = 11.80$, $p = .008$. On average, patients with RUSN+ were tested 26 days later than patients with LUSN+ ($U = 190.5$, $z = -2.76$, $p = .006$) and 12 days later than patients with RUSN− ($U = 1524.5$, $z = -2.55$, $p = .011$), whereas the other subgroups did not differ from each other (LUSN+ vs. LUSN−: $U = 797.5$, $z = -1.52$, $p = .129$; LUSN− vs. RUSN−: $U = 6057$, $z = 0.11$, $p = .909$). Furthermore, the stroke subgroups differed regarding MMSE score, $\chi^2(3) = 16.19$, $p = .001$. The RUSN− group had a higher MMSE score compared to the LUSN− group ($U = 1938$, $z = -3.53$, $p < .001$) and compared to the RUSN+ group ($U = 814$, $z = -2.55$, $p = .011$). No differences were observed between the LUSN− and LUSN+ group ($U = 184.5$, $z = -1.52$, $p = .129$), nor between the LUSN+ and RUSN+ group ($U = 73$, $z = -0.93$, $p = .355$). The groups were comparable regarding BI, $\chi^2(3) = 3.56$, $p = .314$; MI arm, $\chi^2(3) = 3.20$, $p = .362$; and MI leg, $\chi^2(3) = 1.58$, $p = .664$. Finally, a difference was observed in SAN score, $\chi^2(3) = 47.83$, $p < .001$. The LUSN− group obtained a lower SAN score compared to the RUSN− group ($U = 1938$, $z = -6.13$, $p < .001$), and the LUSN+ group obtained a lower score compared to the RUSN+ group ($U = 71$, $z = -3.21$, $p = .001$), indicating more severe language communication deficits in the left brain-damaged patients. No differences in SAN score were seen between the LUSN− and LUSN+ group ($U = 496.5$, $z = -1.00$, $p = .315$) nor between the RUSN− and RUSN+ group ($U = 1005.5$, $z = -1.44$, $p = .149$).

Search organization measures

In Table 5.2, the shape cancellation outcome measures are depicted for all groups. Differences existed between the five groups regarding the omission difference score, $\chi^2(4) = 198.27$, $p < .001$; number of perseverations, $\chi^2(4) = 10.03$, $p = .040$; consistency of search direction, best *r*; $\chi^2(4) = 11.29$, $p = .023$; distance between consecutive cancelled targets, $\chi^2(4) = 51.76$, $p < .001$; and number of intersections, $\chi^2(4) = 50.02$, $p < .001$. Box plots for the organizational measures are depicted in Figure 5.1.

Table 5.2 Mean scores and standard deviations at the organizational measures among the five groups based on the shape cancellation test

Outcome	Controls (n = 37)	LUSN– (n = 115)	RUSN– (n = 108)	LUSN+ (n = 18)	RUSN+ (n = 39)
Perseverations	0.22 (0.71)	0.41 (0.99)	0.50 (2.41)	1.72 (3.10)	0.92 (1.95)
Best r	.88 (.12)	.84 (.18)	.79 (.22)	.78 (.22)	.77 (.20)
Distance	139 (44)	154 (38)	159 (15)	167 (49)	202 (66)
Intersections	0.03 (0.05)	0.05 (0.06)	0.06 (0.06)	0.07 (0.05)	0.14 (0.12)

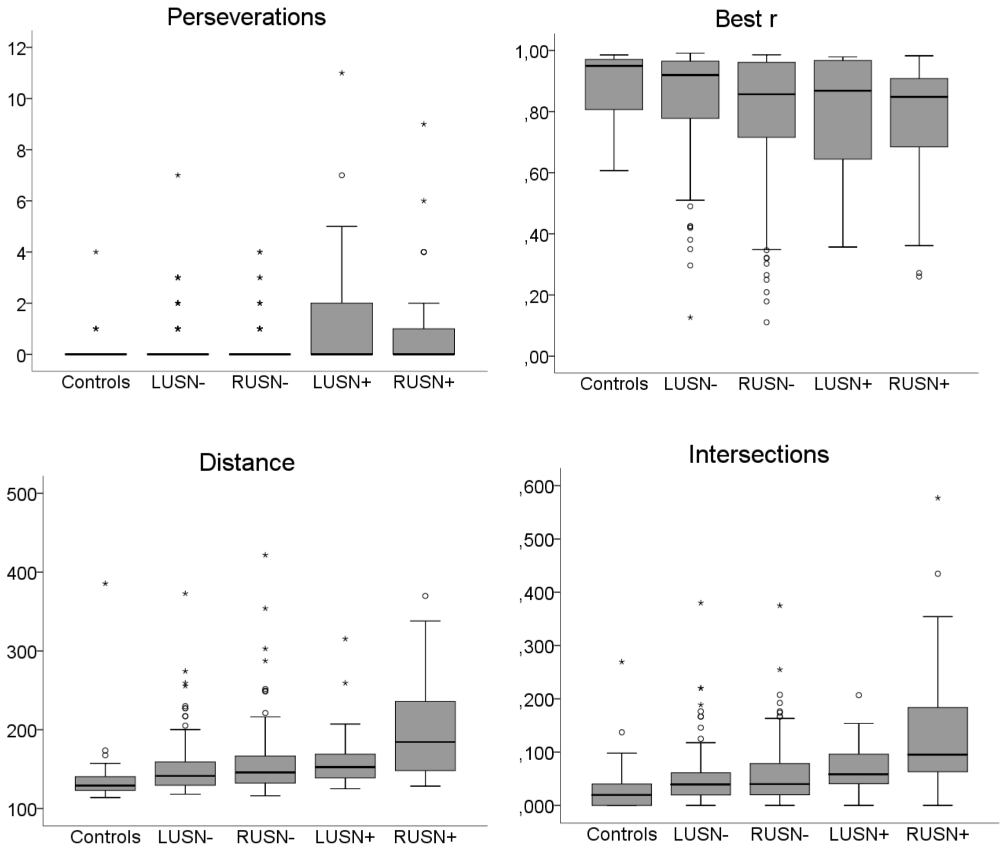

Figure 5.1 Box plots for the number of perseverations, best *r*, distance and number of intersections. Median, quartiles, extreme values and outliers are depicted.

Stroke patients versus healthy controls

Compared with the healthy control group, the LUSN+ ($U = 0$, $z = -6.87$, $p < .001$) and RUSN+ group ($U = 0$, $z = -7.88$, $p < .001$) omitted more targets. No difference in number of omissions was seen for the LUSN− ($U = 1800.5$, $z = -2.04$, $p = .042$) and RUSN− group ($U = 1753$, $z = -1.70$, $p = .089$) compared with the healthy control group. The number of perseverations did not differ between the stroke subgroups and the healthy control group ($U = 238.5$ to 1926, $z = -2.35$ to -0.51, all $p \geq .019$). Furthermore, the consistency of the search direction did not differ between the LUSN-, RUSN-, and LUSN+ groups versus the healthy control group ($U = 248$ to 1914, $z = -2.04$ to -0.92, all $p \geq .042$). Only the RUSN+ group showed a less consistent search direction compared to the healthy control group ($U = 472$, $z = -2.59$, $p = .010$). All stroke subgroups showed a larger distance between consecutive cancelled targets compared with the healthy control group ($U = 125$ to 1186.5, $z = -5.95$ to -3.73, all $p < .001$). In the RUSN−, LUSN+, and RUSN+ groups, a higher number of intersections was observed compared with the healthy control group ($U = 169$ to 1282, $z = -5.71$ to -2.30, all $p \leq .003$). The number of intersections of the patients with LUSN− did not differ from the healthy control patients ($U = 1630$, $z = -2.16$, $p = .030$).

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Left versus right brain-damaged patients

Statistics for these comparisons are depicted in Table 5.3. The LUSN− group omitted as many targets as the RUSN− group ($p = .576$). However, the RUSN+ group tended to omit more targets than the LUSN+ group, although this was not statistically significant ($p = .017$). This trend could indicate that patients in the RUSN+ group showed more severe USN compared with patients in the LUSN+ group. The number of perseverations was comparable between the LUSN− and RUSN− group ($p = .348$) and between the LUSN+ and RUSN+ group ($p = .424$). No difference was seen regarding the consistency of search direction between the LUSN− and RUSN− group ($p = .052$) nor between the LUSN+ and RUSN+ group ($p = .643$). The distance between the consecutive cancelled targets did not differ between the LUSN− and RUSN− group ($p = .361$), nor between the RUSN+ group versus the LUSN+ group ($p = .029$). The LUSN− and RUSN− group showed a comparable number of intersections ($p = .105$), whereas the RUSN+ group showed a higher number of intersections compared to the LUSN+ group ($p = .009$).

Table 5.3 Comparisons of the search organizational measures between left and right brain damaged patients

Outcome	LUSN− vs. RUSN−	LUSN+ vs. RUSN+
Omissions difference score	$U = 6017$, $z = -0.94$, $p = .576$	$U = 216$, $z = -2.38$, $p = .017$
Perseverations	$U = 5899$, $z = -0.94$, $p = .348$	$U = 312$, $z = -0.80$, $p = .424$
Best *r*	$U = 5276$, $z = -1.94$, $p = .052$	$U = 324$, $z = -0.46$, $p = .643$
Distance	$U = 5770.5$, $z = -0.91$, $p = .361$	$U = 224$, $z = -2.18$, $p = .029$
Intersections	$U = 5433.5$, $z = -1.62$, $p = .105$	$U = 198$, $z = -2.63$, $p = .009$*

*Significant with the adjusted level of significance (α = .0125)

USN+ versus USN− patients (shape cancellation test)

As expected, the LUSN+ patients omitted more targets compared to the LUSN− patients ($p < .001$), and the RUSN+ patients omitted more targets compared to the RUSN− patients ($p < .001$; see Table 5.4 for statistics). No difference was seen in amount of perseverations between the LUSN− and LUSN+ group ($p = .057$), nor between the RUSN+ and RUSN− group ($p = .047$). No relation was observed between neglect severity and the number of perseverations ($r = .10$, $p = .484$). The consistency of search direction (best *r*) did not differ between the LUSN+ and LUSN− group ($p = .057$) nor between the RUSN+ and RUSN− group ($p = .298$). Additionally, no relation between neglect severity and consistency of the search direction was found ($r = -.22$, $p = .104$). We observed no difference in distance between consecutive clicked targets between the LUSN+ and LUSN− group ($p = .109$). Interestingly, the RUSN+ group showed a larger distance between consecutive cancelled targets compared to the RUSN− group ($p < .001$). The distance between consecutive cancelled targets was not related to neglect severity ($r = .20$, $p = .128$). Again, no difference in number of intersections was seen between the LUSN− and LUSN+ group ($p = .051$), while the RUSN+ group showed a larger number of intersections compared to the RUSN− group ($p < .001$). Finally, the number of intersections showed a moderate positive correlation with neglect severity ($r = .34$, $p = .009$).

Table 5.4 Comparisons of the search organizational measures between USN+ and USN– patients (shape cancellation test)

Outcome	LUSN– vs. LUSN+	RUSN– vs. RUSN+
Omissions difference score	$U = 0$, $z = -8.13$, $p < .001$*	$U = 0$, $z = -10.36$, $p < .001$*
Perseverations	$U = 818.5$, $z = -8.13$, $p = .057$	$U = 1787$, $z = -1.99$, $p = .047$
Best *r*	$U = 908$, $z = -1.90$, $p = .057$	$U = 1869$, $z = -1.04$, $p = .298$
Distance	$U = 791.5$, $z = -1.60$, $p = .109$	$U = 1120$, $z = -4.33$, $p < .001$*
Intersections	$U = 740$, $z = -1.96$, $p = .051$	$U = 957.5$, $z = -5.05$, $p < .001$*

*Significant with the adjusted level of significance (α = .0125)

USN+ versus USN– patients (line bisection test)

Of all patients, 235 also completed the line bisection test. Patients were regrouped based on results of the line bisection test. The mean values of the shape cancellation measures for each new subgroup, and statistics of the comparisons are depicted in Table 5.5. Again, the LUSN+ group omitted more targets compared to the LUSN– group ($p = .009$) and the RUSN+ group omitted more targets compared with RUSN– group ($p < .001$). No difference was seen regarding the number of perseverations between the LUSN+ and LUSN– group ($p = .116$) nor between the RUSN+ and RUSN– group ($p = .723$). The LUSN– and LUSN+ group did not differ regarding consistency of search direction ($p = .074$), whereas the RUSN+ group searched less consistent compared to the RUSN– group ($p = .009$). The distance between consecutive clicked targets was comparable for the LUSN– and LUSN+ groups ($p = .226$) and for the RUSN+ and RUSN– groups ($p = .035$). Finally, no difference was seen regarding number of intersections between the LUSN– and LUSN+ group ($p = .712$), whereas the RUSN+ group showed a larger number of intersections compared with the RUSN– group ($p = .001$). To summarize, when subgroups were made based on the line bisection test, we observed a difference in search consistency between patients with RUSN+ and RUSN–, which was not seen when subgroups were based on the shape cancellation test. Finally, only when subgroups were based on the shape cancellation test, patients with RUSN+ showed a larger distance than patients with RUSN–. The other results confirm the comparisons between these subgroups when classification was based on the shape cancellation test.

Table 5.5 Mean scores and standard deviations at shape cancellation measures, and comparisons among the four patient subgroups based on the line bisection test

Outcome	LUSN– (n = 75)	LUSN+ (n = 41)	LUSN– vs. LUSN+	RUSN– (n = 61)	RUSN+ (n = 80)	RUSN– vs. RUSN+
Omissions difference score	0.36 (0.71)	1.68 (4.39)	U = 1161.5, z = –2.60, p = .009*	0.34 (0.75)	2.71 (4.63)	U = 1469, z = –4.50, p < .001*
Perseverations	0.37 (1.15)	0.51 (1.00)	U = 1345, z = –1.57, p = .116	0.36 (0.90)	0.88 (3.09)	U = 2380, z = –0.35, p = .723
Best r	.87 (.18)	.81 (.19)	U = 1228, z = –1.79, p = .074	.82 (.20)	.75 (.22)	U = 1816, z = –2.60, p = .009*
Distance	155 (43)	158 (34)	U = 1328, z = –1.21, p = .226	162 (51)	174 (55)	U = 1932, z = –2.11, p = .035
Intersections	0.05 (0.05)	0.05 (0.06)	U = 1474, z = –0.37, p = .712	0.06 (0.05)	0.10 (0.10)	U = 1646, z = –3.31, p = .001*

*Significant with the adjusted level of significance (α = .0125)

Discussion

Our overall aim was to investigate whether disorganized search was related to stroke in general, or to right brain damage or USN in particular. To this aim, we used a shape cancellation test and analysed several outcome measures related to search organization: (1) consistency of search direction, (2) distance between consecutive cancelled targets, and (3) number of intersections with paths between previous cancelled targets. We compared performance between patients with left and right brain damage (L, R) and with and without USN (USN+, USN−) based on the shape cancellation test, resulting in four subgroups: LUSN−, RUSN−, LUSN+, and RUSN+. First, we compared the subgroups with healthy control subjects, and it was found that all four subgroups were on average 15 years older than the healthy control subjects. There is some evidence that age affects visual search (Müller-Oehring, Pfefferbaum, Schulte, Rohlfing, & Sullivan, 2013), but this is mainly related to decline in speed rather than search organization (Geldmacher & Riedel, 1999). We analysed the scores on the organizational measures in relation to age in the current study and observed that only the number of intersections showed a positive trend correlation. However, the LUSN− group did not differ from the healthy control group on this measure, suggesting that something other than age must account for the differences between the other stroke groups and the healthy control group. Regarding the other measures, all stroke subgroups showed a larger distance between consecutive cancelled targets compared to the healthy control group. Finally, only the RUSN+ group searched less consistent in comparison with the healthy control group.

Previously, it was shown that right brain-damaged patients searched less organized compared to left brain-damaged patients (Weintraub & Mesulam, 1988). However, this could be explained by the fact that presumably more patients with USN were present among the right brain-damaged patients (Stone et al., 1993). By splitting patients on both lesion side and USN and comparing these subgroups with each other, we revealed that no differences existed between patients with LUSN− and RUSN−. A difference existed within the patients with USN: the patients with RUSN+ made more omissions, showed a larger distance, and showed a higher number of intersections compared to the patients with LUSN+. Analysing disorganized search in patients with and without USN learned that no differences were seen between the LUSN− and LUSN+ group, whereas the RUSN+ group searched less organized compared to the RUSN− group.

The observation of poorer search organization in patients with RUSN+ compared to patients with RUSN− was replicated when USN groups were determined based on results on the line bisection test. Again, patients with RUSN+ showed a higher number of intersections with paths between previous crossed targets compared to patients with RUSN−. These results suggest that patients with RUSN+ searched less organized compared to patients with RUSN−, regardless of the specific type of USN. However, only when patients were classified based on the shape cancellation test, patients with RUSN+ showed a higher distance than patients with RUSN−, and only when patients were classified based on the line bisection test, patients with RUSN+ differed regarding consistency of search compared to patients with RUSN−. This inconsistent finding could be explained by different cognitive processes underlying performance on each test; cancellation tests have been associated with a more egocentric frame of reference, whereas line bisection may require a combination of both allocentric and egocentric reference frames (Oppenländer et al., 2015). Disturbances of ventral (temporal) information processing, concerning detailed object representations, might lead to allocentric impairment, whereas disorders of the fronto-parietal processing stream, dealing with spatial information, might cause egocentric deficits (Grimsen, Hildebrandt, & Fahle, 2008). Possibly, egocentric deficits resulted in both problems at the line bisection test and less consistent search at the cancellation test.

The different results for the current search organization measures question which of them appears to pinpoint efficient strategy best. The measures of distance and intersections were previously analysed in a study of Rabuffetti et al. (2012), who divided 193 stroke patients in LUSN−, RUSN−, and RUSN+ subgroups and compared them with healthy control subjects. No patients with LUSN+ were present. They observed no differences regarding distance, whereas the number of intersections differed between all groups. The contrary findings regarding distance could be explained by their cancellation template, in which targets were more equally distributed across the stimulus field than in our shape cancellation test, in which targets were distributed in a more columnar fashion (also used by Mark et al., 2004). Both the direction and pattern of the search affected the distance (Figures 5.2 and 5.3). The distance was the smallest in case of a ‘snake pattern’ in the vertical direction, and the largest in case of a ‘typewriter pattern’ in the horizontal direction. Thus, in our study, high scores for distance did not necessarily imply disorganized search, as all four possible choices (i.e., horizontal or vertical direction and a snake or typewriter pattern) were structured. However, the distance could tell something about the difference in pattern and direction choice between the stroke patients and healthy control subjects. The most common cancellation path chosen by the healthy control subjects in the study of Rabuffetti et al. (2012) was in the horizontal direction. In our study, however, we observed that healthy control subjects choose a ‘snake pattern’ in the vertical direction most often, and rarely choose a ‘typewriter pattern’ or the horizontal direction. The patients showed a variety of patterns and directions, which can explain the larger average distance compared to the healthy control group. A possible explanation for the differences in choice of search pattern and direction is that the ‘snake pattern’ in the vertical direction, which was chosen the most by healthy control subjects, was the most efficient cancellation pattern in our specific test (e.g., consecutive targets were the closest). It is likely that stroke patients in general have more difficulty in obtaining a quick proper overview in (complex) spatial layouts, for example due to slowed information processing and/or executive dysfunction (Cumming, Marshall, & Lazar, 2013; de Haan, Nys, & Van Zandvoort, 2006), resulting in

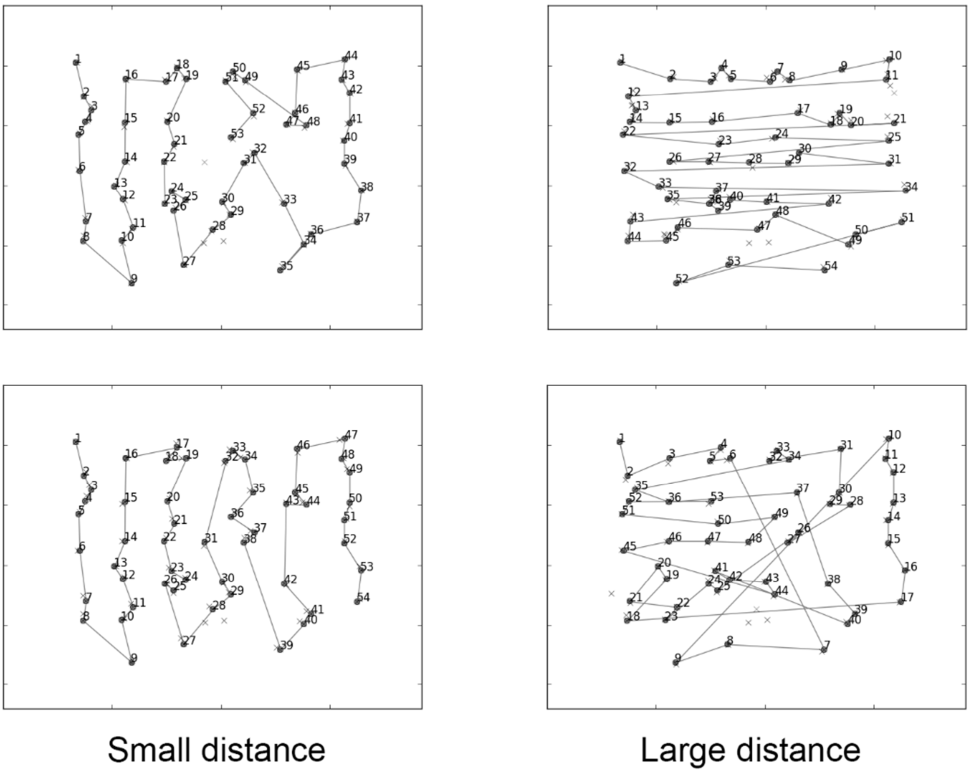


Figure 5.2 Examples of search patterns resulting in small (left images) or large (right images) distance between consecutive cancelled targets.

difficulty in choosing the most efficient pattern.

The measure regarding the consistency of search (best *r*) seems to depict whether one is searching in the same direction during the whole test. In case of a cochlear pattern (Figure 5.4), however, the score is quite low, despite the used pattern is consistent.

Previously, Woods and Mark (2007) reported high convergent validity of the consistency of search direction, distance, and intersections. Despite this finding, we argue that abnormal scores on the first two measures do not *necessarily* imply disorganized search. Both the distance and consistency seem confounded by the choice of search direction and pattern.

To summarize, we conclude that the number of intersections with paths between previously cancelled targets is the most sensitive measure to indicate problems with search organization in a stroke population. This measure reflects the number of path crossings with previous cancellation paths (Figure 5.5). The number of intersections was higher for patients with RUSN−, LUSN+, and RUSN+ versus healthy control subjects. Despite that

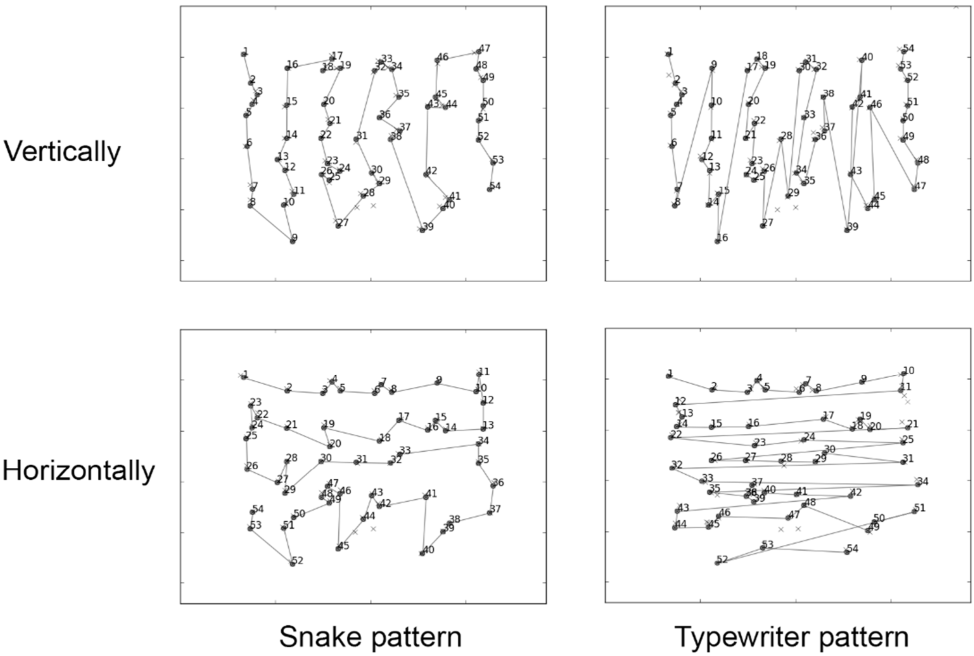


Figure 5.3 Examples of cancellation directions and patterns. Upper and lower images depict two different search directions and left and right images depict two different search patterns.

the number of intersections was largely comparable between the LUSN− and LUSN+ group, only the patients with LUSN− performed comparable with healthy control subjects. Furthermore, the RUSN+ group showed a higher number of intersections compared with the RUSN− and the LUSN+ group. This could be explained by the observation that patients with right brain damage showed more severe USN compared to patients with left brain damage, and neglect severity was related to the number of intersections. Additionally, the RUSN+ group was tested later than the LUSN+ and the RUSN− group, indicating that these patients stayed longer at the hospital before being admitted to the rehabilitation centre. It is known from the literature that right brain-damaged patients with USN are more severe affected after stroke than right brain-damaged patients without USN. For example, USN correlated positively with motor function impairment, visual and tactile sensory loss and anosognosia, and predicted family burden (Buxbaum et al., 2004). Yet, based on the literature, it seems unlikely that poorer outcome after stroke is the most important factor

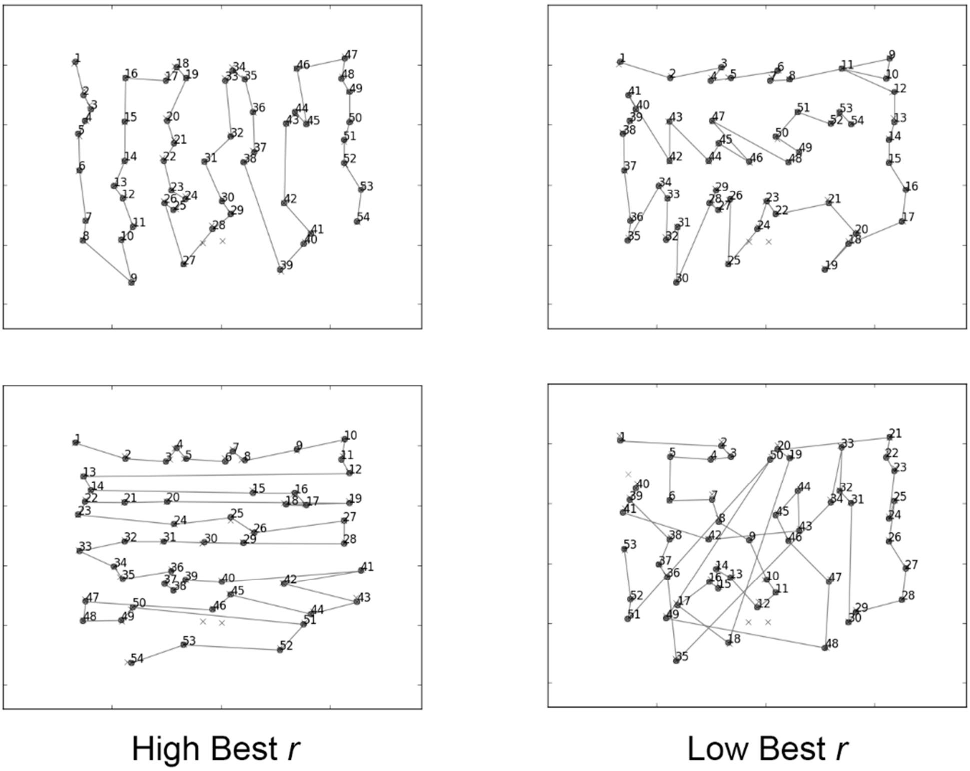


Figure 5.4 Examples of search patterns resulting in high (left images) or low (right images) values for best *r*.

explaining the results, but instead right hemisphere damage (Weintraub & Mesulam, 1988) accompanied by USN is (Rabuffetti et al., 2012; Samuelsson et al., 2002).

Several cognitive and visuospatial factors may contribute to disorganized search in patients with USN. First of all, patients with USN show a spatial bias of attention to the ipsilesional side. For example, they more often make saccades to the ipsilesional side than to the contralesional side (Ro, Rorden, Driver, & Rafal, 2001). In a subset of patients with USN, spatial working memory could be additionally disturbed, due to right posterior parietal damage (Luukkainen-Markkula, Tarkka, Pitkänen, Sivenius, & Hämäläinen, 2011; Malhotra et al., 2005; Pisella et al., 2011; Pisella & Mattingley, 2004). In a study of Malhotra et al. (2005), it was shown that patients with USN were unable to remember whether a spatial location was displayed in a sequence or not. When a patient is unable to keep track of spatial locations during a cancellation test, the same locations will be searched repeatedly, leading to disorganized search. The disturbed underlying mechanism could be

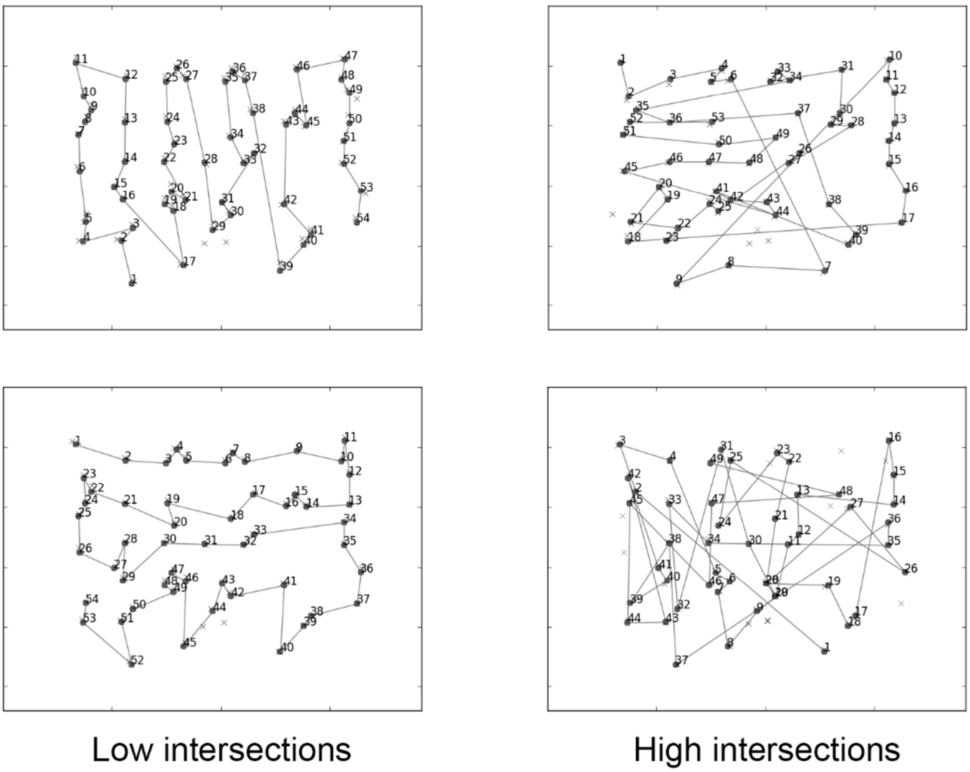


Figure 5.5 Examples of search patterns resulting in low (left images) or high (right images) values for intersections.

spatial remapping, which can be considered as the elementary stage of processing for spatial working memory (Pisella & Mattingley, 2004). At each ocular fixation, the retinotopic maps are renewed in the primary visual areas. The successive maps are integrated in the parietal cortex by remapping processes that provide an updated representation of components of the visual scene. In this way, a stable and spatially relevant representation of the visual scene is maintained (Pisella & Mattingley, 2004). This level of visual space representation is proposed to be located in the right inferior parietal lobule. Damage of the right posterior parietal cortex, including the inferior parietal lobule, disturbs the remapping process. In a normal process of integration, the important information from the previous retinal image is stored and prevented from being overwritten. In case the remapping process is disturbed, the relevant information disappears from awareness and affects the next eye movement (Pisella et al., 2011; Pisella & Mattingley, 2004). In a cancellation test, this could lead to a loss of awareness of targets, even in case these targets were processed earlier during the test. As a consequence, these patients have no clear image of the relative position of targets on the stimulus field. This may cause disorganized search during cancellation tests, expressing in cancelling targets that are distant from each other, changing the cancellation pattern and cross paths between already cancelled targets.

An impairment of visual remapping could also explain perseverations, whereby the marked targets are overwritten by a new visual scene and treated as new targets (Husain et al., 2001). Perseverations have been associated with USN in some studies (Na et al., 1999; Nys, Nijboer, & de Haan, 2008; Nys, Van Zandvoort, Van Der Worp, Kappelle, & De Haan, 2006), but not in others (Rusconi, Maravita, Bottini, & Vallar, 2002). In the current study, both healthy control subjects and stroke patients without USN showed some preservative responses, which has been observed before (Nys et al., 2006), and no significant differences compared to patients with USN were found. The distinctness of the circles that appeared around the targets could have prevented patients with USN to revisit targets more often. In tests whereby the marks are less obvious or absent, patients with USN are provoked to perseverate more (Husain et al., 2001).

Conclusion and implications

In the present study, the patients with RUSN+ were less organized compared to the patients with LUSN+ and RUSN−, which was expressed in a higher number of intersections with previous cancellation paths and a larger distance between consecutive cancelled targets.

The difference between left brain- and right brain-damaged patients within the USN group seemed primarily caused by the degree of USN, which was more severe in the right brain-damaged patients. Furthermore, whereas the patients with LUSN+ deviated from normal performance regarding the number of intersections, patients with LUSN− performed comparable with healthy control subjects. Thus, disorganized search is in particular related to the neglect syndrome and is even more evident in severe USN, which is related to right brain damage.

Identifying search strategies and degree of search organization might gain insight in visuospatial processes and attention of stroke patients. It is useful to evaluate search organization apart from USN during neuropsychological assessment. Patients who do not show USN but do show disorganized search could experience problems during ADL, such as slowness or inefficient searching for personal belongings. Measures of search organization could already be analysed in standard neuropsychological tests. Currently, free software is available to analyse all kinds of computerized cancellation tests and compute organizational measures (Dalmaijer et al., 2014). Future research needs to examine whether search organization can be trained during rehabilitation.

Acknowledgements

This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN.

Chapter 6

The right hemisphere is dominant in organization of visual search - A study in stroke patients

Ten Brink, A. F., Biesbroek, J. M., Kuijf, H., Van der Stigchel, S., Oort, Q., Visser-Meily, J. M. A., Nijboer, T. C. W. (2016). The right hemisphere is dominant in organization of visual search - a study in stroke patients. *Behavioural Brain Research, 304*, 71-79.

Abstract

Cancellation tasks are widely used for diagnosing attentional deficits in stroke patients. A disorganized fashion of target cancellation has been hypothesized to reflect disturbed spatial exploration. In the current study we aimed to examine which lesion locations result in disorganized visual search during cancellation tasks, to determine which brain areas are involved in search organization. A computerized shape cancellation task was administered in 78 stroke patients. As an index for search organization, the amount of intersections of paths between consecutive crossed targets was computed (i.e., intersections rate). This measure is known to accurately depict disorganized visual search in a stroke population. Ischemic lesions were delineated on CT or MRI images. Assumption-free voxel-based lesion-symptom mapping and region of interest-based analyses were used to determine the grey and white matter anatomical correlates of the intersections rate as a continuous measure. The right lateral occipital cortex, superior parietal lobule, postcentral gyrus, superior temporal gyrus, middle temporal gyrus, supramarginal gyrus, inferior longitudinal fasciculus, first branch of the superior longitudinal fasciculus (SLF I), and the inferior fronto-occipital fasciculus, were related to search organization. To conclude, a clear right hemispheric dominance for search organization was revealed. Further, the correlates of disorganized search overlap with regions that have previously been associated with conjunctive search and spatial working memory. This suggests that disorganized visual search is caused by disturbed spatial processes, rather than deficits in high level executive function or planning, which would be expected to be more related to frontal regions.

Introduction

Cancellation tasks are widely used for diagnosis of attention deficits in stroke patients. In these tasks, multiple targets have to be found among distractors and crossed out. Additionally, cancelled targets should not be crossed out twice. An asymmetry in the number of omitted targets between the left versus right half of the page is typically used as an indication for visuospatial neglect, an attentional disorder which is defined as the failure to orient, report or respond to visual stimuli toward the contralesional side of space (Halligan & Marshall, 1993).

Completing a cancellation task in an *organized* way requires a preconceived top-down strategy. Though it is achievable to cancel all targets without adopting a specific strategy, a disorganized fashion of target cancellation has been hypothesized to reflect a disorder in spatial exploration or planning (Mark et al., 2004). For instance, stroke patients show less organized cancellation patterns compared to healthy control subjects (Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016). Moreover, stroke patients with visuospatial neglect have an even less organized visual search pattern compared to stroke patients without neglect (Chédru et al., 1973; Rabuffetti et al., 2012; Samuelsson et al., 2002; Ten Brink, Van der Stigchel, et al., 2016; Warren et al., 2008). Even though the presence of visuospatial neglect seems a marker for a disorganized search pattern in stroke patients, the relation is not straightforward, and neglect and disorganized search seem to be distinct phenomena (Mark et al., 2004). Disorganized visual search during cancellation might reflect a multitude of various deficits, such as disturbed executive function, spatial working memory disorder (remapping problems), deficient inhibition of return, loss of a strategy or plan to guide spatial search, difficulties with disengaging attention from already cancelled targets or a failure to inhibit stimulus-bound motor responses (Mark et al., 2004).

In this study, we aimed to investigate the anatomical correlates of visual search organization. A computerized version of a cancellation task was presented to patients with stroke and used to compute the amount of *intersections* with paths between previous cancelled targets (Dalmaijer et al., 2014; Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016; Woods & Mark, 2007). This measure is thought to best depict organization of visual search in a stroke population (Ten Brink, Van der Stigchel, et al., 2016). We performed voxel-based lesion-symptom mapping (VLSM) and region of interest-based (ROI) analyses within grey and white matter to determine the anatomical correlates of visual search organization, and to learn about the various components of visual search.

Methods

Procedure

The design of this study was retrospective. All clinical tests and imaging were conducted in the setting of standard clinical care. The research and consent procedures were performed in accordance with the standards of the Declaration of Helsinki.

Participants

Patients were selected from a cohort consisting of 357 stroke patients who were consecutive admitted to De Hoogstraat Rehabilitation centre from November 2011 through February 2014. MRI or CT scans were administered in the hospital. At admission to the rehabilitation centre, patients were screened for visuospatial neglect with a cancellation task as part of usual care within the first two weeks, if their condition permitted testing. A stepwise exclusion procedure was applied to these 357 patients according to the following criteria: (1) no data on the shape cancellation task (i.e., unable to understand instructions or unable to perform the task due to motor problems or fatigue; n = 31); (2) diagnosis other than ischemic stroke or delayed cerebral ischemia after subarachnoid haemorrhage (n = 85); (3) no delayed CT (i.e., performed >48 hr after symptom onset) or MRI brain scan available for infarct segmentation (n = 154); (4) no infarct visible on post-stroke imaging (n = 6); and (5) insufficient quality of CT or MRI imaging (n = 2) (Supplementary Figure 6.1).

Clinical characteristics

The following data were obtained on admission to the rehabilitation centre: sex, age, time post-stroke, global cognitive functioning score (Mini-Mental State Examination, MMSE; Folstein et al., 1975), level of independence during daily live activities (Barthel Index; Collin et al., 1988), strength in both upper and lower extremities (Motricity Index; Collin & Wade, 1990), and presence of language communication deficits (“Stichting Afasie Nederland” score, SAN).

Shape cancellation task

The computerized shape cancellation task consisted of 54 small targets (0.6° x 0.6°), 52 large distractors, and 23 words and letters (widths ranging from 0.95° to 2.1° and heights ranging from 0.45° to 0.95°). The stimulus presentation was approximately 18.5° wide and 11° high. Patients were seated 120 cm in front of a monitor and used a computer mouse. They were instructed to click all targets and tell the examiner when they had completed the task. No time limit was given. After each mouse click a small circle appeared at the clicked location and remained on screen, regardless whether a target, distractor, or location in between was clicked (Van der Stoep et al., 2013).

For each patient, all cancelled targets were connected in chronological order. Clicks at other locations were excluded from analyses. Targets that were revisited were included in analyses. The amount of crossings of paths between cancelled targets was computed (i.e., intersections). For each participant the *intersections rate* was computed with the CancellationTools software (Dalmaijer et al., 2014). The intersections rate depicts the total amount of path intersections divided by the amount of cancellations that are not immediate revisits, resulting in a value ranging from 0 (no intersections) to 1 (maximum amount of intersections). An organized search pattern includes as few intersections as possible. That is, a high number of intersections would reflect less organized visual search (Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016). See Figure 6.1 for the target stimuli layout and examples of organized versus disorganized search.

The convergent validity of the intersections rate was good, as observer ratings of disorganized search during a cancellation task were highly correlated with the intersections

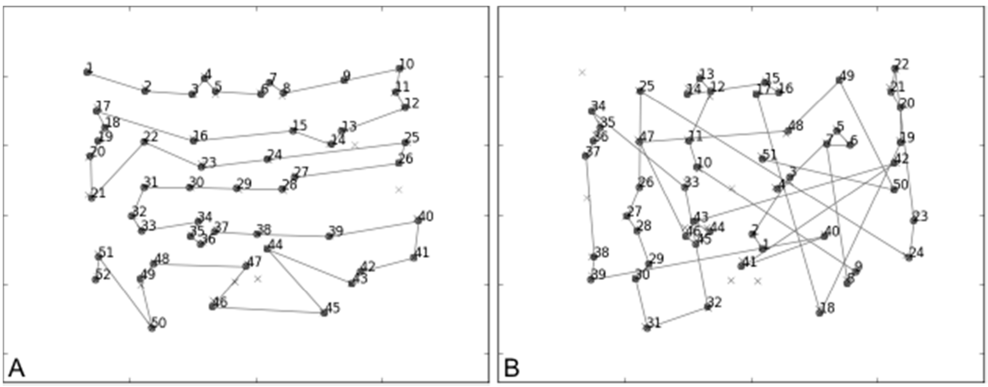


Figure 6.1 Examples of search patterns. Search patterns resulting in low (A) or high (B) values for intersections.

rate (r = .87; Woods & Mark, 2007).

In order to assess the robustness of the VLSM results with the intersections rate as continuous measure, we additionally performed VLSM using norm-based dichotomized performance on the shape cancellation task and a qualitative lesion subtraction analysis. In order to dichotomize the intersections rate, we used the scores of 37 healthy control subjects (Ten Brink, Van der Stigchel, et al., 2016). The threshold was set at their mean score plus 2.5 *SD*. Stroke patients with an intersections rate above this threshold were assigned to the disorganized search group, whereas the other stroke patients were assigned to the organized search group.

Generation of lesion maps

The procedure for the generation of lesion maps has been previously described elsewhere and is only summarised here (Biesbroek et al., 2016; Biesbroek, van Zandvoort, Kappelle, et al., 2014; Biesbroek, van Zandvoort, Kuijf, et al., 2014). Infarcts were manually segmented on transversal slices of either follow-up CT (n = 49), or on T2 FLAIR sequences of MRI scans (n = 29) by a trained rater who was blinded to the cancellation data (JMB). Infarct segmentations were transformed to the Montreal Neurological Institute (MNI)-152 template (Fonov et al., 2009) using the following procedure. All registrations were performed with the elastix toolbox for registration (Klein et al., 2010). An age-specific brain template was used (Rorden et al., 2012), which included a CT and T1 MRI template in the same coordinate space. T2 FLAIR scans were transformed to their corresponding T1 scan using a linear registration. The T1 scans were transformed to the T1 MRI template, with a linear registration followed by a non-linear registration. The registration of the CT scans to the CT template was performed using an in-house developed algorithm, which is described elsewhere (Kuijf et al., 2013). The age-specific T1 MR template was transformed to the T1 MNI-152 template, with a linear and a non-linear registration. All computed transformations were composed into a single transformation step - transforming from source CT/MRI to template CT/MRI to MNI-152 - that was used to align the infarct maps directly to the MNI-152 template. The intermediate registration step using the age-specific CT/MRI template served to improve the quality of the registration by providing a better match between patient and template. Quality checks of the registration results were performed by comparing the native scan to the lesion map in MNI space. For 44 patients, the co-registered lesion maps were manually adjusted to correct for slight registration errors using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron) by JBM.

Statistical analysis

First, clinical characteristics of patients who showed a disorganized search pattern were statistically compared to those of patients who showed an organized search pattern, using Mann-Whitney and Chi-Square tests, since data was not normally distributed. Additionally, the lesion locations between the groups with organized versus disorganized search patterns were compared with a Fischer Exact test. The alpha-level that was used to determine significance was $p = .05$ (two-tailed).

We used hypothesis-free VLSM to determine the relationship between the intersections rate and the presence of a lesion in a given voxel (Rorden & Karnath, 2004). VLSM was performed using non-parametric mapping (Rorden, Bonilha, et al., 2007); settings: *t*-test, univariate analysis, only including voxels that were damaged in at least four patients, before and after adjusting for total infarct volume. Correction for multiple testing was performed using a false discovery rate threshold (FDR) with $q < .01$ before, and $q < .05$ after adjusting for total infarct volume, because adjustment for total infarct volume decreases statistical power (Biesbroek, van Zandvoort, Kuijf, et al., 2014).

We chose to use the continuous intersections rate as outcome measure for our main analysis rather than dichotomized performance, because dichotomization tends to reduce statistical power and does not take into account the degree of disorganization of visual search. To assess the robustness of our results, we additionally performed a qualitative lesion subtraction analysis and repeated the VLSM analysis using the norm-based dichotomized performance on the shape cancellation task as outcome measure (settings: Liebermeister statistic, FDR $q < .05$; Rorden, Karnath, et al., 2007).

Next, we complemented the VLSM analysis with ROI-based linear regression models, to quantify the impact of region lesion volumes on the intersections rate. For this purpose, 96 cortical and 21 subcortical non-overlapping regions were extracted from the probabilistic Harvard-Oxford atlas (threshold at 0.25; Desikan et al., 2006). Regions for subdivisions of gyri were merged into a single variable, thereby reducing the total number of regions to 89 (e.g., the anterior and posterior division of the inferior temporal gyrus were merged into a single region). Additionally, regions for 16 white matter tracts were extracted from the probabilistic Johns Hopkins University White Matter Tractography Atlas (threshold at 0.25; Hua et al., 2008). This atlas contains a total of 20 regions, of which only the regions for the superior longitudinal fasciculus (SLF) were not included for this study. Regions for the three branches of the SLF (I-III) were extracted from a previously described subcortical atlas to study the impact of infarcts in this tract for each branch separately (Rojkova et al., 2016). All regions were projected on the VLSM results and the amount of voxels with a statistically significant correlation within each region was quantitatively assessed. Regions that appeared to be involved in the intersections rate based on the VLSM results (operationally defined as at least 5% of tested voxels having a statistically significant association between the presence of a lesion and intersections rate, with a total of no less than 100 significant voxels; similar to Biesbroek, van Zandvoort, Kappelle, et al., 2014; Biesbroek, van Zandvoort, Kuijf, et al., 2014), were selected as ROIs for the linear regression analyses. For every patient, the infarct volumes within these ROIs were computed and entered as independent variables in a linear regression model with the z-score of intersections rate as dependent variable, before and after adding total infarct volume to the model.

Finally, an additional sensitivity analysis was conducted, in which the VLSM and ROI-based analyses were restricted to patients with ischemic stroke.

Results

A total of 79 patients met our inclusion criteria. One patient had an intersections rate of 6 *SD* above the mean of all patients, and was considered an outlier. This patient was excluded from all analyses. Of the 78 remaining stroke patients, five patients suffered from delayed cerebral ischemia after subarachnoid haemorrhage and 73 patients from ischemic stroke. Clinical characteristics of the patients are provided in Table 6.1. A disorganized visual search pattern was found in 21.5% of patients. The z-scores of intersections rate ranged from –0.94 to 0.57 with a median of –0.60 in the organized search group, and from 0.90 to 3.77 with a median of 1.47 in the disorganized search group. There were no significant differences between patients showing an organized search pattern versus patients showing a disorganized search pattern regarding sex, age, time post-stroke, MMSE, Barthel Index, Motricity Index Arm, Motricity Index leg, or SAN score (all $p \geq .064$).

Table 6.1 Mean scores of clinical characteristics and outcome measures on the shape cancellation task in relation to search organization

Outcome	*n*	Organized search (*SD*)	*n*	Disorganized search (*SD*)	Statistics
Sex (% male)	62	62.9%	16	62.5%	$X^2(1, N = 78) = 0.001$, $p = .976$
Age (years)	62	57.11 (11.10)	16	55.38 (16.50)	$U = 494.5$, $z = -0.02$, $p = .985$
Time post-stroke (days)	62	32.02 (24.25)	16	43.75 (39.0)	$U = 416$, $z = -0.99$, $p = .322$
MMSE (0-30)	44	26.82 (2.90)	12	25.33 (4.70)	$U = 226.5$, $z = -0.76$, $p = .448$
Barthel Index (0-20)	54	13.22 (5.84)	12	9.92 (5.30)	$U = 213$, $z = -1.85$, $p = .064$
Motricity Index Arm (0-100)	53	65.74 (39.20)	12	54.42 (38.32)	$U = 259$, $z = -1.03$, $p = .064$
Motricity Index Leg (0-100)	52	73.02 (35.94)	12	63.42 (38.32)	$U = 252.5$, $z = -1.07$ $p = .286$
SAN (1-7)	56	5.54 (1.86)	12	5.83 (1.53)	$U = 321$, $z = -0.25$, $p = .799$
Intersections rate (0-1)	62	.056 (.048)	16	.288 (.087)	$U = 0$, $z = -6.15$, $p < .001$*

Abbreviations: MMSE, Mini-Mental State Examination; SAN, Stichting Afasie Nederland.

* Statistically significant with an alpha-level of $p < .05$

The lesion locations in the organized and disorganized search groups are shown in Table 6.2. Of patients with disorganized visual search patterns, 75% had a lesion in the right hemisphere compared to 36% of patients with organized search patterns (p = .023).[3]

Table 6.2 Location of ischemic lesion in relation to search organization

	Organized search (n = 62)	Disorganized search (n = 16)
Left hemisphere	26 (41.9%)	2 (12.5%)
Right hemisphere	22 (35.5%)	12 (75%)
Infratentorial	7 (11.3%)	0 (0%)
Multiple locations	7 (11.3%)	2 (12.6%)

Voxel-based lesion-symptom mapping

The spatial distribution of infarcts and the voxels that were damaged in at least four patients are depicted in Figure 6.2A. The VLSM analysis identified a substantial number of right hemispheric voxels with a statistically significant association between the presence of a lesion and higher intersections rate (i.e., disorganized search), mostly located in right parietal, occipital and temporal cortices (Figure 6.2B). The exact location of these significant voxels is provided in Table 6.3. Several voxels remained significant after correction for total infarct volume, which were located in the right lateral occipital cortex, superior parietal lobule and postcentral gyrus, and, within the white matter, the right inferior longitudinal fasciculus (ILF), the first branch of the right SLF (SLF I), and the right inferior fronto-occipital fasciculus (IFO) (Figure 6.2C).

The lesion overlay and subtraction plots of patients with a disorganized and organized search pattern are shown in Figure 6.3A-C. When the VLSM analysis was repeated using norm-based dichotomized performance (disorganized versus organized search) as the dependent variable instead of the intersections rate, the results were essentially the same: lesions in right parietal, occipital and temporal regions were again associated with disorganized search (Figure 6.3D).

[3] The two patients in the disorganized search group who had an isolated lesion in the left hemisphere were both right handed. Lesions were located both cortical and subcortical: frontoparietal in the first patient, and frontal, parietal and temporal in the second patient.

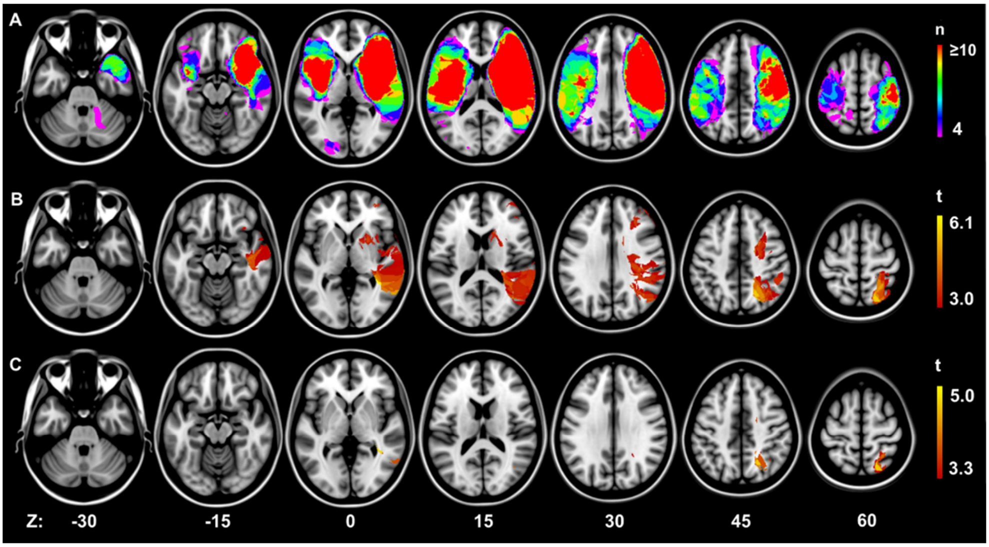


Figure 6.2 Distribution of lesions and VLSM results. The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. (A) Voxels that are damaged in at least four patients are plotted. The coloured bar indicates the number of patients with a lesion for a given voxel. (B) Map of the voxelwise association (*t*-statistic) between the presence of a lesion and the intersections rate. Voxels exceeding the FDR threshold (q = .01) are rendered on a scale from red to yellow. (C) Map of the voxelwise association (*t*-statistic) between the presence of a lesion and the intersections rate, adjusted for total infarct volume. Voxels exceeding the FDR threshold (q = .05) are rendered on a scale from red to yellow.

Table 6.3 Voxel-based lesion-symptom mapping results for intersections rate: tested and significant voxels for each ROI

Anatomical regions	Patients with lesion (*n*)[a]	Region size in voxels (*n*)	Tested voxels (*n*)	Significant voxels before correction for total infarct volume (*n* [%])	Significant voxels after correction for total infarct volume (*n* [%])
Grey matter					
R superior temporal gyrus	22	5509	5500	3697 (67.22%)	0
R middle temporal gyrus	16	20577	11690	7150 (61.16%)	0
R superior parietal lobule	19	11800	8635	4843 (55.98%)	28 (0.32%)
R lateral occipital cortex	22	54872	21936	11630 (53.02%)	796 (3.63%)
R heschl's gyrus	26	2223	2223	974 (43.81%)	0
R angular gyrus	17	11704	11657	4879 (41.85%)	0
R supramarginal gyrus	25	16304	16300	6572 (40.32%)	0
R planum Temporale	22	3538	3538	1396 (38.69%)	0
R planum polare	24	2998	2998	519 (17.31%)	0
R caudate	27	4165	4041	643 (15.91%)	0
R parietal operculum cortex	23	4290	4290	549 (12.80%)	0
R frontal pole	24	65201	26520	3131 (11.81%)	0
R postcentral gyrus	26	25920	18473	1508 (8.16%)	6 (0.03%)
R insular cortex	29	10801	10801	804 (7.44%)	0
R pallidum	24	2147	2143	154 (7.19%)	0
R middle frontal gyrus	25	22069	21289	1270 (5.97%)	0
White matter					
R ILF	23	4486	2255	1367 (60.62%)	45 (2.0%)
R SLF I	12	2301	559	207 (37.03%)	33 (5.90%)
R SLF II	25	1930	1930	179 (9.27%)	0
R SLF III	29	5185	5185	945 (18.23%)	0
R IFO	31	7880	5643	1397 (24.76%)	151 (2.68%)

R ATR	31	8153	4948	913 (18.45%)	0
R CST	28	5021	3169	439 (13.85%)	0

Abbreviations: ATR, anterior thalamic radiation; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; R, right; SLF: superior longitudinal fasciculus.

Note. Regions for which our criterion for involvement was met (i.e., 5% of tested voxels had a statistically significant association between the presence of a lesion and intersections rate, with a minimum of 100 significant voxels) are shown here; the remaining regions are not shown.

[a] Indicates how many of the 78 patients had a lesion (≥1 voxel) within the specified region

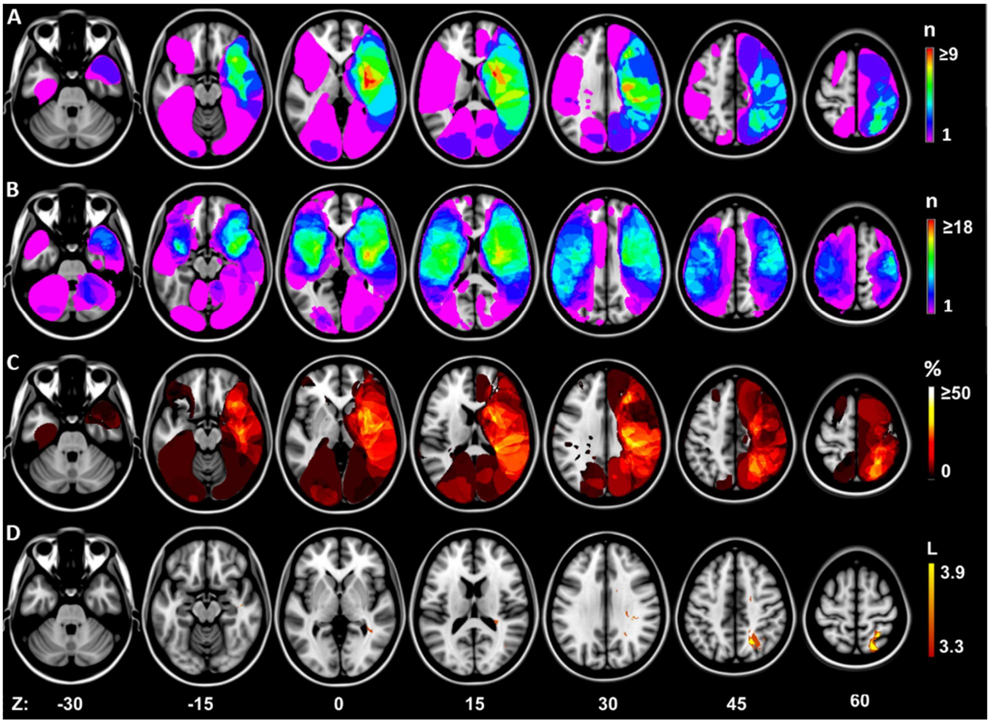


Figure 6.3 Lesion overlay and subtraction plots, and VLSM results with dichotomized performance as outcome. The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. The overlay plots show the number of patients with a lesion for a given voxel separately for patients who showed a disorganized (A) and an organized (B) visual search pattern. (C) The lesion subtraction plot depicts which voxels are more frequently affected in patients who showed a disorganized search pattern compared to patients who showed an organized search pattern. (D) Map of the voxel wise Liebermeister statistic with norm-based dichotomized performance (i.e., disorganized versus organized search). Voxels that were damaged significantly more often in patients who showed a disorganized search pattern are rendered on a scale from red to yellow (corrected for multiple testing with FDR q = .05).

Region of interest-based analyses

In total, 16 grey matter and 7 white matter right hemispheric regions were selected as ROIs, based on the VLSM results (listed in Table 6.3). In the linear regression model with *z*-scores for intersections rate as the dependent variable, we first added age and sex, which explained only 1.3% in variance and was not significant (p = .617). Subsequently, total infarct volume was added, which explained an additional 10.2% in variance (p = .005). Finally, infarct volumes within the 23 ROIs were added to the model (Table 6.4). Infarct volumes within the right middle and superior temporal gyrus, lateral occipital cortex, superior parietal lobule, supramarginal gyrus, ILF, SLF I, and IFO were correlated with intersections rate, independent of total infarct volume. The increase in explained variance on top of age, sex and total infarct volume was highest for infarct volume within the right SLF I (increase in explained variance of 13.8%; p = .001). The results of the linear regression analyses without correction for total infarct volume are reported in Supplementary Table 6.1.

Finally, in the sensitivity analyses in which the VLSM and ROI-based analyses were restricted to patients with ischemic stroke, the results were essentially the same (Supplementary Figure 6.2 and Supplementary Table 6.2).

Table 6.4 Results of linear regression models with intersections rate as outcome after correction for total infarct volume

Model	Independent variables	R^2	$p\Delta R^2$	*B* (95% CI)
1	Age, sex	.013	.617	
2	Model 1 + total infarct volume	.115	.005*	0.003 (0.001 to 0.006)
3a	Model 2 + R superior temporal gyrus	.167	.036*	0.024 (0.014 to 0.394)
3b	Model 2 + R middle temporal gyrus	.169	.033*	0.093 (0.008 to 0.178)
3c	Model 2 + R superior parietal lobule	.222	.002*	0.179 (0.066 to 0.292)
3d	Model 2 + R lateral occipital cortex	.212	.004*	0.050 (0.017 to 0.083)
3e	Model 2 + R heschl's gyrus	.159	.055	0.341 (–0.008 to 0.689)
3f	Model 2 + R angular gyrus	.160	.054	0.086 (–0.001 to 0.172)
3g	Model 2 + R supramarginal gyrus	.161	.049*	0.067 (0.000 to 0.134)
3h	Model 2 + R planum Temporale	.153	.074	0.221 (–0.022 to 0.463)
3i	Model 2 + R planum polare	.137	.183	0.201 (–0.097 to 0.500)
3j	Model 2 + R caudate	.135	.200	0.150 (–0.081 to 0.382)
3k	Model 2 + R parietal operculum cortex	.144	.125	0.145 (–0.041 to 0.331)
3l	Model 2 + R frontal pole	.123	.411	0.018 (–0.025 to 0.060)
3m	Model 2 + R postcentral gyrus	.123	.433	0.023 (–0.035 to 0.081)
3n	Model 2 + R insular cortex	.135	.202	0.043 (–0.023 to 0.109)
3o	Model 2 + R pallidum	.133	.225	0.235 (–0.148 to 0.619)
3p	Model 2 + R middle frontal gyrus	.117	.750	0.009 (–0.046 to 0.064)
3q	Model 2 + R ILF	.179	.020*	0.450 (0.072 to 0.827)
3r	Model 2 + R SLF I	.253	.001*	1.744 (0.714 to 2.773)
3s	Model 2 + R SLF II	.126	.358	0.277 (–0.321 to 0.875)
3t	Model 2 + R SLF III	.138	.165	0.118 (–0.050 to 0.286)
3u	Model 2 + R IFO	.167	.037*	0.186 (0.012 to 0.359)
3v	Model 2 + R ATR	.140	.151	0.146 (–0.054 to 0.347)
3w	Model 2 + R CST	.133	.229	0.209 (–0.135 to 0.554)

Abbreviations: ATR, anterior thalamic radiation; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; R, right; SLF: superior longitudinal fasciculus.

Note. The explained variance (R^2) in intersections rate is given for each model with the corresponding *p*-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (*B*) applies to the change in *z*-score of intersections rate for every 1 ml increase in infarct volume with higher *z*-score meaning more disorganized search.

* Statistically significant with an alpha-level of $p < .05$

Discussion

In this study, we aimed to find the anatomical correlates of visual search organization by using a computerized version of a cancellation task and applying lesion-symptom mapping in a sample of 78 stroke patients. The intersections rate, based on the amount of path crossings between consecutive cancelled shapes, was used as a measure for visual search organization (Dalmaijer et al., 2014; Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016). We found a clear dominance for the right hemisphere in search organization. The grey matter regions that were related to disorganized search during cancellation were located within the parietal lobe (i.e., the right postcentral gyrus, superior parietal lobule and supramarginal gyrus), within the temporal lobe (i.e., the right superior and temporal gyri), and within the occipital lobe (i.e., the right lateral occipital cortex). The white matter tracts that were associated with search organization were the right inferior longitudinal fasciculus (ILF), the first branch of the right superior longitudinal fasciculus (SLF I), and the right inferior fronto-occipital fasciculus (IFO).

The contribution of these different areas is informative with regards to the various components underlying visual search organization. We found that lesions in the posterior part of the right cortex (parietal, occipital and temporal areas) were associated with disorganized search. These results are reminiscent of findings with patients with posterior cortical atrophy (PCA), a neurodegenerative condition. In PCA, patients show reductions of grey matter in regions of the occipital and parietal lobes followed by areas in the temporal lobe (Crutch et al., 2012), with an asymmetry between hemispheres (greater reductions right than left). PCA patients show visuospatial and visuoperceptual impairments, deficits in working memory and features of Bálint's syndrome (including simultanagnosia, oculomotor apraxia, optic ataxia, environmental agnosia, Crutch et al., 2012; disorganized ocular exploration, and revisiting behaviour, Pisella, Biotti, & Vighetto, 2015). The overlap in associated brain areas indicates that these functions might be involved in the organization of search.

Some of the specific brain areas that were associated with disorganized search in the current study have previously been related to spatial remapping and spatial working memory (Pisella et al., 2011). For instance, lesions within the right inferior parietal lobule (Chechlacz, Rotshtein, & Humphreys, 2014) and the right parietal and insula regions (Malhotra et al., 2005) are related to impaired performance in spatial working memory tasks. Furthermore, the superior and inferior parietal lobule have been related to sustained attention to spatial locations (Malhotra, Coulthard, & Husain, 2009). Spatial working memory and sustained attention are important in both conjunctive search tasks and cancellation tasks: previously searched locations have to be memorized throughout the trial, and the visual representation of the world must be updated, to prevent searching the same location repeatedly and to search all locations within the stimulus field. In conjunctive search, participants have to find a target which cannot be distinguished from distractors on the basis of a single feature (Treisman & Gelade, 1980). Not surprisingly, in a recent study, lesions in similar brain areas as those that were found in the current study were associated with poor conjunctive search: occipital (middle occipital gyrus), posterior parietal (angular gyrus), and temporal cortices (superior and middle temporal gyri extending to the insula), and white matter damage within pathways including the IFO, the internal capsule and the SLF (Humphreys & Chechlacz, 2015). A lesion in the IFO also correlated with intersections rate in the current study. The association of the IFO with disorganized search and conjunctive search may be explained by the fact that this white matter tract is important in peripheral vision and processing of visual spatial information (Martino & De Lucas, 2014; Schmahmann, Smith, Eichler, & Filley, 2008). The IFO connects the frontal lobe with the postero-lateral temporal, parietal and occipital lobes, including the superior parietal lobule, which was associated with search organization in the present study.

The most obvious finding to emerge from our analyses is that of all patients who showed a disorganized search pattern, 75% had an unilateral lesion in the right hemisphere. In prior research, right hemispheric dominance was found for spatial working memory and spatial remapping (Pisella et al., 2011), as well as for the related attentional disorder visuospatial neglect (Danckert & Ferber, 2006; Karnath et al., 2004; Molenberghs & Sale, 2011). To summarize, it is likely that deficits in spatial working memory and sustained attention to spatial locations contribute to disorganized visual search.

Another important finding was that infarcts in the superior temporal gyrus correlated with intersections rate. Danckert and Ferber (2006) speculated that the superior temporal gyrus might be important for integrating different faculties (e.g., encoding locations and identities of objects, spatial working memory, reorienting attention) into a coherent whole, which is necessary to perceive a stable environment and search according to an organized pattern. This speculation was based on several findings. First, the superior temporal gyrus is thought to be involved in reorienting of attention, as patients with lesions at this site have longer RTs to contralesional targets following ipsilesional cues (Danckert & Ferber, 2006; Friedrich, Egly, Rafal, & Beck, 1998). Additionally, the superior temporal gyrus is involved in encoding the locations and identities of objects, which was found by measuring regional cerebral blood flow while subjects engaged in retrieval or perceptual matching of spatial location and object identity (Danckert & Ferber, 2006; Köhler, Moscovitch, Winocur, Houle, & McIntosh, 1998). Finally, neurophysiological recordings have learned that polysensory neurons, found in the superior temporal sulcus, are multimodal, they have large receptive fields, and receive input from both the dorsal and ventral stream.

In the current study it was also shown that lesions in the SLF I and in the right temporoparietal junction (TPJ; involving the right middle and superior temporal gyrus and right supramarginal gyrus) correlated with intersections rate. Given the known role of these areas in the dorsal and ventral attentional systems, this may indicate that an impairment in search organization is related to a damaged ventral and/or dorsal attentional system, or to a lack of proper communication. On the one hand, the dorsal network is involved in top-down attention (i.e., the voluntary deployment of attention), and contains the intraparietal sulcus and the frontal eye fields of each hemisphere. The SLF I is known to connect dorsal frontoparietal areas: this white matter tract connects the posterior supramarginal gyrus and the posterior portion of the superior temporal gyrus (Martino & De Lucas, 2014), brain areas that were both associated with search organization in the current study. Additionally, the SLF I is connected to the inferior parietal lobule.

On the other hand, the ventral network is involved in bottom-up attention (i.e., the reorientation to unexpected events), and contains the TPJ and the ventral frontal cortex (Danckert & Ferber, 2006; Vossel, Geng, & Fink, 2014). Whereas the SLF III connects ventral frontoparietal areas (Thiebaut de Schotten et al., 2011), the SLF II is known to connect the dorsal and ventral networks, and may act as a modulator for the dorsal network (Thiebaut de Schotten et al., 2011). Although a lesion in the SLF II is a predictor of neglect (Thiebaut de Schotten et al., 2014), damage to the SLF II and SLF III was not related to disorganized search. It is possible, however, that damage in one system could affect the functionality in structurally intact remote networks (Vossel et al., 2014). For example, prior research in stroke patients showed that structural damage of ventral areas was accompanied by a functional impairment in the dorsal network (Vossel et al., 2014). It is possible, therefore, that disorganized search could result from both impairments in the ventral and dorsal attentional system, as flexible interaction between the two systems is necessary for the dynamic control of attention (Vossel et al., 2014).

The final white matter tract that was related to search organization, was the ILF. The ILF connects the anterior part of the temporal lobe to the occipital lobe (Martino & De Lucas, 2014). The direct pathway of the ILF connects with the superior and middle temporal gyri, which were also associated with organized search. Furthermore, the inferior temporal gyrus, fusiform gyrus, parahippocampal gyrus, amygdala, and hippocampus are connected with the ILF. Among other functions, the ILF has been implicated in face recognition, visual perception, reading and language (Martino & De Lucas, 2014). However, the exact role of the ILF remains unclear.

The anatomy of neglect matches the TPJ-ventral frontal cortex system (Corbetta & Shulman, 2002; Danckert & Ferber, 2006; Karnath et al., 2004; Molenberghs & Sale, 2011). Neglect is thought to result from interacting impairments, including biases in attentional orienting and exploratory motor behaviours, deficits in spatial remapping and a deficit of spatial working memory (Danckert & Ferber, 2006). All these impairments contribute to neglect, but it is currently unknown whether these distinct types of impairment always co-occur in neglect (Danckert & Ferber, 2006; Pisella & Mattingley, 2004). The overlap between the brain areas related to neglect and disorganized search are in line with prior research, which showed that neglect is a marker for disorganized search (Mark et al., 2004; Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016). These studies have used the difference in number of omissions between left and right on a shape cancellation task as a measure of neglect and related this difference to the intersections rate. In the study of Mark et al. (2004), only patients with left-sided neglect were included. Ten Brink, Van der Stigchel, et al. (2016) found that both left and right brain-damaged patients with neglect searched less organized than stroke patients without neglect. However, search was least organized in right brain-damaged patients, either with or without neglect. To conclude, despite the close relationship, disorganized visual search and neglect seem to be distinct phenomena which can occur independently of each other (Mark et al., 2004; Ten Brink, Van der Stigchel, et al., 2016).

In prior research, planning and executing an organized search pattern has been linked to executive function. Search cancellation outcome measures, including the amount of intersections, are even called “executive organization measures on cancellation” (Mark et al., 2004; Woods & Mark, 2007). This link seems plausible in the sense that spatial working memory and sustained attention, which are relevant for organized search, are sometimes considered aspects of executive function (Alvarez & Emory, 2006). Executive function is highly associated with the frontal lobes (Alvarez & Emory, 2006; Hanna-Pladdy, 2007), but in the current study no relation was found between frontal lesions and disorganized visual search during cancellation. Furthermore, the right hemispheric dominance indicates involvement of spatial working memory and attentional deficits rather than an executive disorder. Possibly, this could be explained by the simplicity of cancellation tasks. No complex higher order cognitive flexibility, social tact, or problem-solving are required, which are more typical components of executive functioning (Alvarez & Emory, 2006; Hanna-Pladdy, 2007). During cancellation tasks, the 'plan' that has to be executed is straightforward, and several strategies (e.g., following a specific pattern or cancelling targets that are in close proximity of each other) could result in an organized search pattern (Ten Brink, Van der Stigchel, et al., 2016).

In the current study, both patients with ischemic stroke and delayed cerebral ischemia after subarachnoid haemorrhage were included. It is thought that subarachnoid haemorrhage can affect brain function both at a macroscopic and microscopic, synaptic level (Al-Khindi, Macdonald, & Schweizer, 2010). These microscopic changes might be functionally relevant but could not be taken into account in our analyses. However, the reproduction of our main findings in the sensitivity analyses in which only patients with ischemic stroke were included indicates that this has not affected our results.

Furthermore, hemianopic patients were not excluded. It could be argued that visual search disorders simply result from hemianopic field loss. We consider this unlikely, however, since visual search is more severely affected in hemianopic patients with right brain damaged compared to hemianopic patients with left brain damage, which supports the idea a visual field deficit alone cannot account for disturbed visual search (Machner, Sprenger, Sander, et al., 2009; Zihl, 1995).

Limitations

A limitation of the current study is that VLSM can only be applied to voxels that are damaged in a certain amount of patients. As a consequence, we cannot draw any conclusions regarding regions that were affected in less than four patients.

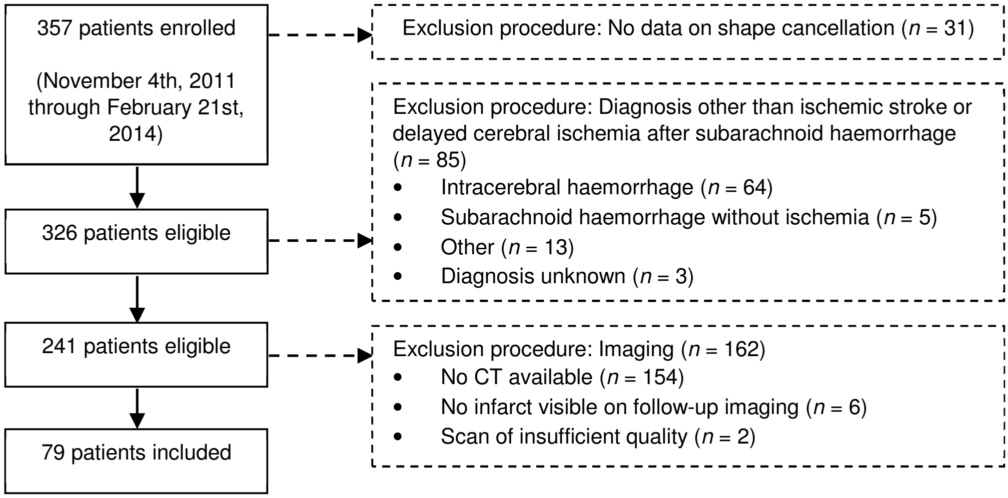
Furthermore, VLSM constitutes a region-based approach to determining the anatomical correlates of a given function, as opposed to a network-based approach. In other words, VLSM does not take into account the possibility that a lesion at a given location may cause dysfunction in other nodes of a functional brain network, impairing processes other than those mediated by neurons at the lesion location (the distributed injury hypothesis; Corbetta et al., 2005). For example, it is now known that many fibre pathways connect cortical areas that are relevant for spatial orienting and exploration (Suchan et al., 2014) and it has been argued that disorders such as neglect are better explained by dysfunctional cortical networks than by lesions of specific brain regions (Corbetta & Shulman, 2011; Smith, Clithero, Rorden, & Karnath, 2013). We therefore included ROIs for major fibre pathways in our region of interest-based analyses.

Conclusions

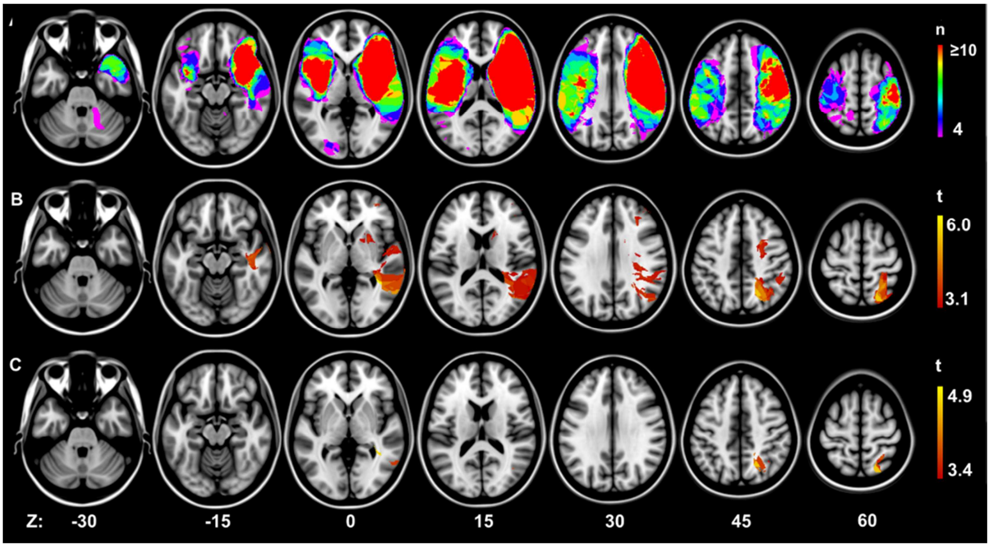
This study has shown that post-stroke disorganized visual search during cancellation tasks is most strongly related to the right hemisphere, in particular the temporoparietal junction (TPJ). These correlates overlap with regions that have previously been associated with conjunctive search, spatial remapping and working memory, the ventral and dorsal attentional systems and visuospatial neglect. This suggests that disorganized visual search during cancellation tasks is caused by disturbed spatial processes, rather than complex higher order executive function or planning, which is more related to frontal regions.

Acknowledgements

This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN, and the “Revalidatiefonds” under grant R2012134 to TCWN and JMAVM. We would like to thank Krista Huisman, Jorine van der Pas and Charlotte Pasma for their help in collecting the data. We would like to thank Prof. Geert Jan Biessels for fruitful discussion of the results.



Supplementary Figure 6.1 Flowchart of patient inclusion



Supplementary Figure 6.2 Sensitivity analysis: distribution of ischemic lesions and VLSM results restricted to 73 patients with ischemic stroke. The results of the remaining 73 patients are projected on the MNI-152 template. The right hemisphere is depicted on the right. (A) Voxels that are damaged in at least four patients are plotted. The coloured bar indicates the number of patients with a lesion for a given voxel. (B) Map of the voxelwise association (*t*-statistic) between the presence of a lesion and the intersections rate. Voxels exceeding the FDR threshold (q = .01) are rendered on a scale from red to yellow. (C) Map of the voxelwise association (*t*-statistic) between the presence of a lesion and the intersections rate, adjusted for total infarct volume. Voxels exceeding the FDR threshold (q = .05) are rendered on a scale from red to yellow.

Supplementary Table 6.1 Results of linear regression models with intersections rate as outcome, without correction of total infarct volume

Model	Independent variables	R^2	$p\Delta R^2$	*B* (95% CI)
1	Age, sex	.013	.617	
2	Model 1 + total infarct volume	.115	.005*	0.003 (0.001 to 0.006)
3a	Model 1 + R superior temporal gyrus	.114	.001*	0.273 (0.115 to 0.430)
3b	Model 1 + R middle temporal gyrus	.150	.001*	0.124 (0.052 to 0.195)
3c	Model 1 + R superior parietal lobule	.206	< .001*	0.212 (0.113 to 0.312)
3d	Model 1 + R lateral occipital cortex	.187	< .001**	0.061 (0.030 to 0.091)
3e	Model 1 + R heschl's gyrus	.139	.001*	0.473 (0.187 to 0.758)
3f	Model 1 + R angular gyrus	.097	.002*	0.120 (0.045 to 0.195)
3g	Model 1 + R supramarginal gyrus	.145	.001*	0.091 (0.038 to 0.145)
3h	Model 1 + R planum Temporale	.130	.002*	0.319 (0.117 to 0.521)
3i	Model 1 + R planum polare	.110	.006*	0.339 (0.101 to 0.577)
3j	Model 1 + R caudate	.089	.015*	0.259 (0.051 to 0.467)
3k	Model 1 + R parietal operculum cortex	.116	.080	0.227 (0.073 to 0.380)
3l	Model 1 + R frontal pole	.092	.013*	0.041 (0.009 to 0.073)
3m	Model 1 + R postcentral gyrus	.092	.013*	0.055 (0.012 to 0.098)
3n	Model 1 + R insular cortex	.063	.009*	0.075 (0.019 to 0.131)
3o	Model 1 + R pallidum	.045	.021*	0.415 (0.066 to 0.765)
3p	Model 1 + R middle frontal gyrus	.068	.039*	0.045 (0.002 to 0.087)
3q	Model 1 + R ILF	.165	< .001*	0.570 (0.261 to 0.880)
3r	Model 1 + R SLF I	.216	< .001*	2.045 (1.115 to 2.974)
3s	Model 1 + R SLF II	.096	.011*	0.590 (0.141 to 1.039)
3t	Model 1 + R SLF III	.115	.005*	0.193 (0.061 to 0.325)
3u	Model 1 + R IFO	.160	.001*	0.232 (0.104 to 0.361)
3v	Model 1 + R ATR	.109	.006*	0.238 (0.071 to 0.405)
3w	Model 1 + R CST	.102	.008*	0.377 (0.100 to 0.654)

Abbreviations: ATR, anterior thalamic radiation; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; R, right; SLF, superior longitudinal fasciculus.

Note. The explained variance (R^2) in intersections rate is given for each model with the corresponding *p*-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (*B*) applies to the change in *z*-score of intersections rate for every 1 ml increase in infarct volume with higher *z*-score meaning more disorganized search.

* Statistically significant with an alpha-level of $p < .05$

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Supplementary Table 6.2 Sensitivity analyses: results of linear regression models with intersections rate as outcome after correction for total infarct volume restricted to 73 patients with ischemic stroke

Model	Independent variables	R^2	$p\Delta R^2$	*B* (95% CI)
1	Age, sex	.023	.439	
2	Model 1 + total infarct volume	.136	.004*	0.004 (0.001 to 0.006)
3a	Model 2 + R superior temporal gyrus	.210	.014*	0.235 (0.049 to 0.421)
3b	Model 2 + R middle temporal gyrus	.202	.021*	0.099 (0.016 to 0.183)
3c	Model 2 + R superior parietal lobule	.230	.005*	0.168 (0.052 to 0.284)
3d	Model 2 + R lateral occipital cortex	.232	.005*	0.048 (0.015 to 0.081)
3e	Model 2 + R heschl's gyrus	.178	.068	0.327 (–0.025 to 0.680)
3f	Model 2 + R angular gyrus	.192	.034*	0.093 (0.007 to 0.178)
3g	Model 2 + R supramarginal gyrus	.197	.027*	0.074 (0.009 to 0.140)
3h	Model 2 + R planum Temporale	.182	.055	0.233 (–0.005 to 0.472)
3i	Model 2 + R planum polare	.175	.077	0.269 (–0.030 to 0.567)
3j	Model 2 + R caudate	.166	.125	0.178 (–0.051 to 0.406)
3k	Model 2 + R parietal operculum cortex	.164	.140	0.140 (–0.047 to 0.327)
3l	Model 2 + R frontal pole	.151	.276	0.023 (–0.019 to 0.065)
3m	Model 2 + R postcentral gyrus	.147	.349	0.027 (–0.030 to 0.084)
3n	Model 2 + R insular cortex	.157	.200	0.044 (–0.024 to 0.111)
3o	Model 2 + R pallidum	.162	.154	0.273 (–0.105 to 0.651)
3p	Model 2 + R middle frontal gyrus	.139	.638	0.013 (–0.041 to 0.067)
3q	Model 2 + R ILF	.211	.014*	0.470 (0.100 to 0.839)
3r	Model 2 + R SLF I	.269	.001*	1.768 (0.764 to 2.773)
3s	Model 2 + R SLF II	.152	.265	0.332 (–0.257 to 0.922)
3t	Model 2 + R SLF III	.158	.183	0.115 (–0.056 to 0.285)
3u	Model 2 + R IFO	.195	.029*	0.191 (0.020 to 0.362)
3v	Model 2 + R ATR	.165	.131	0.153 (–0.047 to 0.352)
3w	Model 2 + R CST	.153	.253	0.198 (–0.145 to 0.541)

Abbreviations: ATR, anterior thalamic radiation; CST, corticospinal tract; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; R, right; SLF, superior longitudinal fasciculus.

Note. The explained variance (R^2) in intersections rate is given for each model with the corresponding *p*-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (*B*) applies to the change in *z*-score of intersections rate for every 1 ml increase in infarct volume with higher *z*-score meaning more disorganized search.

* Statistically significant with an alpha-level of $p < .05$

6

Chapter 7

What does it take to search organized? The cognitive correlates of search organization during cancellation after stroke

Ten Brink, A. F., Visser-Meily, J. M. A., Nijboer, T. C. W. (In press). What does it take to search organized? The cognitive correlates of search organization during cancellation after stroke. *Journal of the International Neuropsychological Society.*

Abstract

Objective. Stroke could lead to deficits in organization of visual search. Cancellation tests are frequently used in standard neuropsychological assessment and appear suitable to measure search organization. The current aim was to evaluate which cognitive functions are associated with cancellation organization measures after stroke. *Methods*. Stroke patients admitted to inpatient rehabilitation were included in this retrospective study. We performed exploratory factor analyses to explore cognitive domains. A digital shape cancellation test (SC) was administered, and measures of search organization (intersections rate and best *r*) were computed. The following cognitive functions were measured by neuropsychological testing: neglect (SC, line bisection; LB, Catherine Bergego Scale; CBS, and Balloons Test), visuospatial perception and construction (Rey Complex Figure Test, RCFT), psychomotor speed (Trail Making Test; TMT-A), executive functioning/working memory (TMT-B), spatial planning (Tower Test), rule learning (Brixton Test), short-term auditory memory (Digit Span Forward; DSF), and verbal working memory (Digit Span Backward; DSB). *Results*. In total, 439 stroke patients were included in our analyses. Four clusters were separated: “Executive functioning” (TMT-A, TMT-B, Brixton Test, and Tower Test), “Verbal memory” (DSF and DSB), “Search organization” (intersections rate and best *r*) and “Neglect” (CBS, RCFT copy, Balloons Test, SC, and LB). *Conclusions*. Search organization during cancellation, as measured with intersections rate and best *r*, seems a distinct cognitive construct compared to existing cognitive domains that are tested during neuropsychological assessment. Administering cancellation tests and analysing measures of search organization could provide useful additional insights into the visuospatial processes of stroke patients.

Introduction

Humans are constantly engaged in searching for visual information in the world around them (Mort & Kennard, 2003). Being able to perform complex daily activities such as driving or spatial orientation is highly dependent on the quality of visual search (Shinoda, Hayhoe, & Shrivastava, 2001). Brain damage could lead to disturbed search organization (Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016), which is related to difficulties in daily life activities (Machner, Sprenger, Sander, et al., 2009). Deficits in search organization are, therefore, important to detect in clinical populations.

Measures to detect potential search organization deficits are generally not used in clinical practice. However, object cancellation tests – frequently used in standard neuropsychological assessment, especially to detect visuospatial neglect – are suitable to measure search organization (Dalmaijer et al., 2014; Huang & Wang, 2008; Ten Brink, Van der Stigchel, et al., 2016; Woods & Mark, 2007). During such tests, participants have to mark multiple targets on a template. The total number of missed targets is used as an indication for deficits in visual perception and attention, whereas the difference in omitted targets between the left and right side of the stimulus field can be used as an indication for lateralized inattention (Wilson et al., 1987). Measures that provide insight in the degree of search organization, however, can also be extracted from such tests. Search organization measures during cancellation include the number of path crossings, consistency, and distance. The number of path crossings between consecutive cancelled targets (i.e., intersections rate), for example, can be used as an indication of the degree of disorganized search. Another measure of search organization regards the consistency of the overall search pattern (i.e., best *r*), which indicates whether one searched in the same direction throughout the test, for example in a columnar manner or row after row. Finally, the average distance between consecutive cancelled targets can be computed, with a lower distance between targets reflecting more organized search compared to a higher distance (Dalmaijer et al., 2014; Mark et al., 2004; Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016).

In the current study, we aimed to unravel the cognitive functions associated with search organization during cancellation in stroke patients. Whereas healthy participants typically show organized, symmetrical search patterns (Huang & Wang, 2008; Rabuffetti et al., 2012; Samuelsson et al., 2002; Warren et al., 2008), stroke patients tend to search less organized (Chatterjee et al., 1992; Donnelly et al., 1999; Ten Brink, Van der Stigchel, et al., 2016). More specific, stroke patients with right hemispherical damage are more likely to exhibit disorganized visual search during cancellation compared to patients with left hemispherical damage (Rabuffetti et al., 2012; Ten Brink, Biesbroek, et al., 2016; Weintraub & Mesulam, 1988). The cognitive processes associated with search organization, as measured with intersections rate and best *r*, are, however, largely unknown. Knowledge regarding the associations between measures of search organization and common neuropsychological tests is potentially helpful in interpretation of impairment of established cognitive domains and the association to, in this case, quality of visual search.

We evaluated the association between intersections rate and best *r* with other cognitive domains that were measured by means of clinically validated neuropsychological tests. To address this aim, we performed exploratory factor analyses in a sample of stroke patients as, in addition to the aforementioned clinical value, we expected sufficient variation across test performances compared to, for example, a sample of healthy subjects. We focused on intersections rate and best *r*, as they appear to be sensitive to measure search organization in a stroke population (Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016), and have high convergent validity (Woods & Mark, 2007). We did not include the average distance, as this measure is additionally influenced by the *direction* of search next to the organization of search (Ten Brink, Van der Stigchel, et al., 2016).

Prior studies suggest an association between neglect and disorganized search (Rabuffetti et al., 2012; Samuelsson et al., 2002; Ten Brink, Van der Stigchel, et al., 2016), although this association has not always been reported (Mark et al., 2004). We included cancellation and line bisection (LB) tests, the most commonly used tests to measure neglect (Ferber & Karnath, 2001), and observations of neglect in activities of daily living (ADL). Related to neglect is the quality of visual perception and construction, which might be important for search organization (Mark et al., 2004). To assess visual perception and construction, we included the Rey Complex Figure Test (RCFT). Furthermore, we included a test that is closely related to visual search (Singh et al., 2017), but also executive functioning: the Trail Making Test (TMT). Although the TMT and cancellation test both measure visual search, the TMT regards search *speed* instead of *organization*. Next, search organization might relate to executive functioning, since it would require some form of planning (Dalmaijer et al., 2014; Mark et al., 2004). Executive functioning, however, entails several sub functions. We included tests that measure (among other functions) spatial planning and rule learning (i.e., Tower Test and Brixton Test). We did not necessarily expect an association between disorganized search and these higher-order executive functions. An association between visual search and (spatial) working memory, however, has been described (lesion: Humphreys & Chechlacz, 2015; Ten Brink, Biesbroek, et al., 2016; behaviour: Singh et al., 2017). As our study was retrospective, the choices of the neuropsychological tests were restricted to the available data. No measures of *visuospatial* working memory were available. Instead, measures of short-term auditory memory and verbal working memory were included to test potential associations with the memory domain in general.

In all our selected neuropsychological tests (except the verbal memory tests), a motor response was required. We, therefore, reran analyses in patients with high arm motor strength to evaluate whether associations were not distorted by impaired motor functioning. Finally, a right-hemisphere dominance exists for visuo-perception and spatial attention. Analyses were, therefore, repeated for subgroups based on lesion side, to gain additional insight in underlying cognitive processes of search organization within these subgroups.

Methods

Participants

We retrospectively used routinely collected data of stroke patients who were admitted for inpatient rehabilitation in De Hoogstraat Rehabilitation centre, The Netherlands, between November 2011 and June 2017. Inclusion criteria for the current study were: (1) clinical diagnosed symptomatic stroke, first or recurrent; (2) unilateral lesion (to be able to perform sub analyses with left and right hemisphere patients); (3) age of at least 18 years; (4) data on the shape cancellation test (SC) available; and (5) data on at least four of the selected tests available. Patients were excluded when the neglect screening and neuropsychological assessment were administered with more than two weeks in between, as spontaneous neurobiological recovery and/or acquired compensation strategies during cognitive rehabilitation might lead to discrepancies in performance.

Procedure and tests

At admission, the rehabilitation physician noted age, sex, level of education, stroke date, stroke history (first, recurrent), aetiology (ischemic, haemorrhagic, subarachnoid haemorrhage), hemisphere of stroke (left, right, bilateral), Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), presence of language communication deficits ("Stichting Afasie Nederland" score; SAN), Motricity Index, and Barthel Index.

Patients were invited for a neglect screening and a neuropsychological assessment as part of usual care. During the neglect screening, a SC and LB were administered. Additionally, patients' behaviour during basic activities of daily living was observed and scored by a nurse (Catherine Bergego Scale; CBS). Regarding the neuropsychological assessment, we selected the Balloons Test as an additional measure for neglect, the RCFT copy for visuospatial perception and construction, the TMT-A for psychomotor speed, the TMT-B for executive functioning/working memory, the Tower Test for spatial planning, the Brixton Test for rule learning, and the Digit Span for short-term auditory memory (Forward; DSF) and verbal working memory (Backward; DSB). These tests were selected as they (a) reflect different cognitive functions, so the major cognitive domains are represented; and (b) were assessed most frequently, resulting in a relatively large group of patients who performed at least four tests. Due to limited taxability, fatigue or verbal impairments, not all tests were administered in each patient.

The research and consent procedures were performed in accordance with the standards of the Declaration of Helsinki and the research protocol was approved by the Ethics Committee of De Hoogstraat Rehabilitation.

Demographic and clinical characteristics

Education level was assessed using seven categories of a Dutch classification system, according to Verhage, 1 being the lowest (less than primary school) and 7 being the highest (academic degree) (Verhage, 1964).

Global cognitive functioning was screened with either the MMSE (Folstein et al., 1975) or the MoCA (Nasreddine et al., 2005). Both tests globally assess cognitive functioning. Scores range from 0 (no items right) up to 30 (all items right). We converted MMSE scores into MoCA scores to create a single, pooled MoCA score. We applied the following formula: MoCA = (1.124 * MMSE) – 8.165 (Solomon et al., 2014).

The quality of communication was measured with the SAN (Deelman et al., 1981). Scores range from 1 (no communication through language possible) to 7 (speech and understanding of language are unimpaired).

Motor strength for the upper and lower extremity was assessed with the Motricity Index (Collin & Wade, 1990), a short 3-item test to assess the loss of strength in a limb. Scores range from 0 (no activity, paralysis) up to 33 (maximum normal muscle force) for each extremity. In the case of 99 points, one point is added to reach a total score of 100.

Functional independence was measured with the Barthel Index (Collin et al., 1988), which measures the extent to which patients can function independently in their ADL. Scores range from 0 (completely dependent) up to 20 (completely independent).

Neglect screening

Shape cancellation. The digitized SC consisted of 54 small targets (0.6° x 0.6°), 52 large distractors, and 23 words and letters (widths ranging from 0.95° to 2.1° and heights ranging from 0.45° to 0.95°), presented on a computer monitor (Van der Stoep et al., 2013). The stimulus presentation was approximately 18.5° wide and 11° high. Patients were instructed to click on all targets. After each mouse click, a small circle appeared at the clicked location and remained on the screen. No time limit was given.

We computed the number of lines that crossed paths between previously cancelled targets, divided by the total number of cancellations that were not immediate revisits (i.e., intersections rate; formulas are described in Dalmaijer et al., 2014, Eqs. [3-8]). An organized search pattern includes as few intersections as possible, resulting in a low value for intersections rate (Figure 7.1).

In addition, we computed whether patients searched consistently in one direction during the whole test (Mark et al., 2004). We calculated the Pearson correlation coefficient (r) from the linear regression of the x- or y-values of all marked locations relative to the order in which they were marked. The highest absolute correlation of these two (best r) was selected to represent the degree to which calculations were pursued orthogonally (formulas are described in Dalmaijer et al., 2014, Eq. [9]). Best r ranges from 0 (inconsistent search) to 1 (consistent search; Figure 7.1). Finally, we computed the absolute omission difference score, as an indication for neglect. All measures were computed using the CancellationTools software (Dalmaijer et al., 2014).

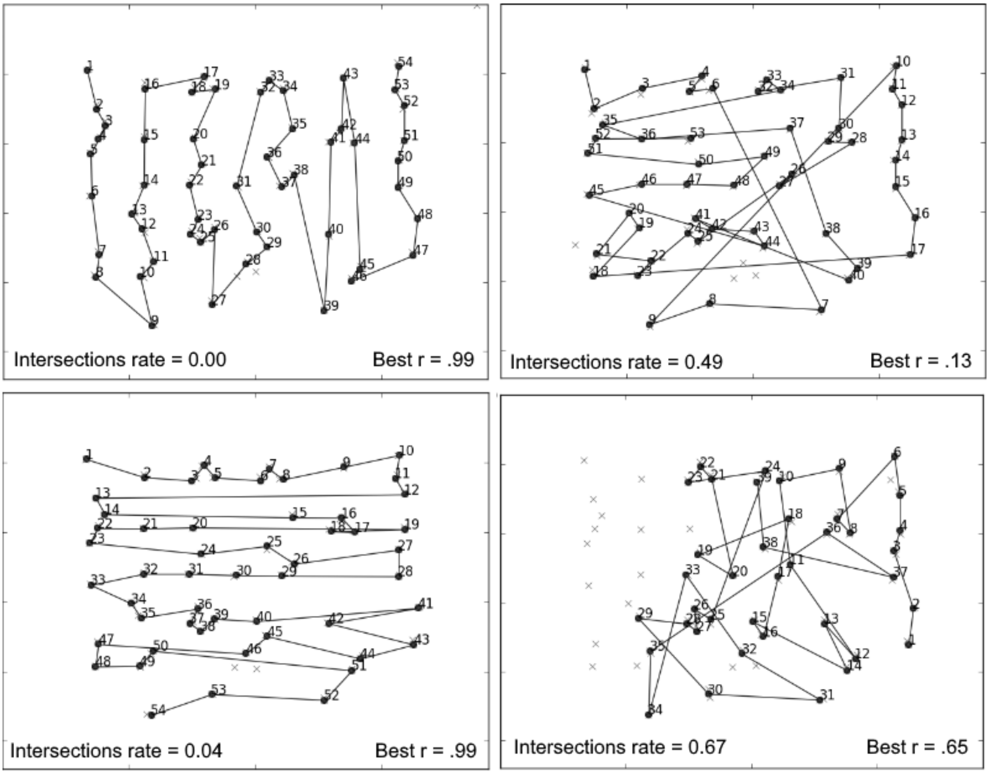

Figure 7.1 Representative examples of search patterns and values of intersections rate and best *r*, obtained by four patients who were included in the current study. Black dots indicate cancelled targets. The numbers indicate the chronological order of the cancelled targets. The paths between cancelled targets depict the search pattern. Missed targets are depicted by an "X". Note that the middle two targets were used as an example, and not included in our analyses.

Line bisection. This test consisted of three horizontal lines (22° long and 0.2° thick) that were presented upper right, lower left, and in the horizontal and vertical centre of a computer screen (Van der Stoep et al., 2013). The amount of horizontal shift between lines was 15% of the line length. The stimulus presentation was approximately 19° wide and 5.7° high. Patients had to mark the midpoint of each line. The three lines were presented four times in a row, after which the absolute average deviation from the midpoint was calculated of all trials, ranging from 0° (no neglect) to 11° (severe neglect).

Catherine Bergego Scale. The CBS is an observation scale for neglect in ADL (Azouvi et al., 2003; Ten Brink et al., 2013). It assesses performance in personal, peripersonal, and extrapersonal space. For 10 items, neglect severity has to be scored, resulting in a total score of 0 (no neglect) to 30 (severe neglect). A score of ≥6 is usually considered as an indication for neglect.

Neuropsychological assessment

Balloons Test. This test is designed to detect visual inattention (Edgeworth, Robertson, & McMillan, 1998). In subtest B, 180 balloons (circles with a vertical line in the lower part) and 20 circles are presented on an A3 paper. Participants have to mark all circles. The laterality score of subtest B (ranging from 0 to 50%, higher scores indicating better performance) was used as an outcome measure for neglect.

Rey Complex Figure Test. The RCFT copy was designed to diagnose disorders in visuospatial perception and visuospatial construction (Biesbroek, van Zandvoort, Kuijf, et al., 2014; Bouma, Mulder, Lindeboom, & Schmand, 2012). Participants are asked to copy the Rey Complex Figure. The accuracy of the drawing is scored based on clearly defined criteria. The total score ranges from 0 (none of the elements were accurately copied) to 36 (perfectly accurate copy).

Trail Making Test. The TMT-A subtest is used to examine psychomotor speed. It consists of a set of 25 circles that contain numbers (1 to 25). Instructions are to connect the circles in ascending order as fast as possible (Bouma et al., 2012). In the TMT-B subtest, executive functioning is examined. The participant has to alternate between numbers and letters (1 – A – 2 – B, etc.). For both subtests, the total duration is recorded.

Tower Test. The Tower Test (Delis, Kaplan, & Kramer, 2007) measures spatial planning, rule learning, inhibition of impulsive and perseverative responding, and the ability to establish and maintain an instructional set. Participants are presented with a board containing three vertical pegs, and five disks with varying diameters. At each of nine trials, an example tower has to be built, and the participant has to obey certain rules. The total score is based on a scoring system which depends on the number of steps per trial (range 0-30), with higher scores indicating better performance.

Brixton Test. The Brixton Spatial Anticipation Test ("Brixton Test") is a visuospatial sequencing test with rule changes (Burgess & Shallice, 1997). Participants are presented with 56 pages, each containing an array of 10 circles set in two rows of five, with each circle numbered from 1 to 10. One of the circles is filled with a blue colour. The participant is shown one page at the time. The position of the blue circle differs per page, and participants have to indicate where they think the blue circle will be located on the next page. The locations are governed by a series of simple rules that change without warning. The total number of errors was computed (range 0-55).

Digit Span. The Digit Span subtest from the WAIS-III-NL and WAIS-IV-NL consists of two parts: DSF and DSB (Wechsler, 2012). The test administrator reads out loud a series of digits. Each part consists of eight items of each two series, that increase in length up to a maximum of 10 digits. During the DSF, short-term auditory memory is measured, and the participant has to repeat the sequence in the same order. During the DSB, the participant has to repeat the items backward to measure verbal working memory. The longest sequence that was correctly repeated was used as an outcome measure (range 2-10).

Statistical analyses

All analyses were carried out in IBM SPSS Statistics version 23 (IBM Corp., 2015). We used descriptive statistics to report demographic and clinical characteristics, and test scores. In addition, we reported Pearson correlation coefficients (r) between all variables.

We performed an explorative factor analysis (Principal Axis Factoring) to unravel the underlying structure of the outcome variables in the model. We applied an oblimin rotation (Direct Oblimin), as we believe dimensions to be correlated. Variables were: intersections rate, best r, SC omission difference score, LB (average deviation), CBS (total score), Balloons Test (laterality score), RCFT copy (total score), TMT-A, TMT-B (duration in seconds), Tower Test (total score), Brixton Test (number of errors), DSF and DSB (longest sequence). All values were measured on a continuous scale. Since for many patients data on one or more tests was missing, we used the option “Exclude cases pairwise”. Data points that were 3.5 *SD* from the mean on one or more outcome measures were considered outliers and excluded from all analyses.

Analyses were repeated for patients with right and left brain damage separately, and for patients with high motor function (defined as a Motricity Index score of ≥66 and being able to use the dominant hand).

Results

Participants

Of 883 stroke patients, 472 met the inclusion criteria and were included in the current study (Figure 7.2). Demographic and clinical characteristics are depicted in Table 7.1. In 68% of patients, the neglect screening and neuropsychological assessment were performed within the same week. In Table 7.2, descriptive scores on the neuropsychological tests are provided. With respect to the measures of search organization, 21% of patients scored outside the normal range regarding intersections rate (based on the average [0.03] + 2 *SD* [0.05] of healthy control subjects), and 18% obtained an abnormal best *r* score (based on the average [0.88] + 2 *SD* [0.12] of healthy control subjects) (Ten Brink, Van der Stigchel, et al., 2016). Of all patients, 33 patients were outliers and were removed from all analyses. Of the 439 included patients, 92% could use their dominant hand to perform the neuropsychological tests.

See Supplementary Table 7.1 for demographic and clinical characteristics, and Supplementary Table 7.2 for descriptive scores on the neuropsychological tests for the subgroups (i.e., patients with right-sided brain damage, left-sided brain damage, high motor scores; all without outliers).

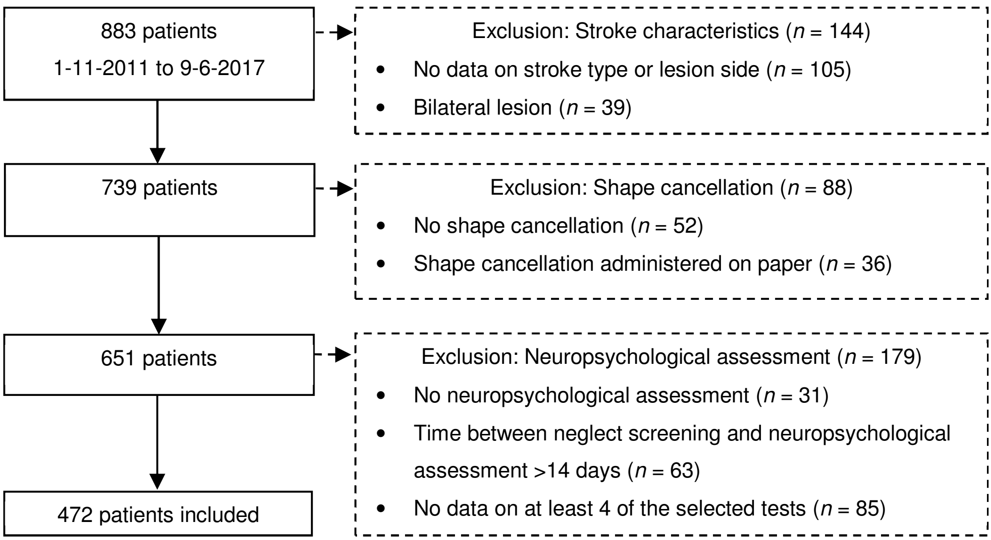

Figure 7.2 Flowchart of patient inclusion.

Table 7.1 Clinical characteristics at admission to rehabilitation, median scores (IQR) or frequencies [%]

Outcome	*N*[1]	*Mdn* (IQR) or *N* [%]	Min	Max
Age, in years	472	60 (15)	20	84
Sex	472			
- Male		283 [60%]		
- Female		189 [40%]		
Level of education (1-7)	472	5 (2)	1	7
Days post-stroke[2]	472	22 (13)	5	386
Delay between neglect screening and neuropsychological assessment	472			
- ≤ 1 week		321 (68%)		
- > 1 week		151 (32%)		
Aetiology	472			
- Ischemic		352 [74.6%]		
- Intracerebral haemorrhage		102 [21.6%]		
- Subarachnoid haemorrhage		18 [3.8%]		
Lesion side	472			
- Left		212 [44.9%]		
- Right		260 [55.1%]		
Stroke history	472			
- First		325 [68.9%]		
- Recurrent		44 [9.3%]		
- Unknown		103 [21.8%]		
MoCA (0-30)	336	23 (5)	3	29
SAN (1-7)	376	6 (2)	1	7
Motricity Index arm (0-100)	375	76 (56)	0	100
Motricity Index leg (0-100)	373	80 (45)	0	100
Barthel Index (0-20)	362	14 (9)	0	20

Abbreviations: MoCA, Montreal Cognitive Assessment; SAN, Stichting Afasie Nederland.

[1]Group sizes differ since not all clinical data were available for all patients.

[2]Days post-stroke at the time of the neglect screening.

Table 7.2 Mean scores, standard deviations, ranges of scores and number of outliers on visual search measures and neuropsychological tests

Outcome	*N*[1]	*M* (*SD*)	Min	Max	Outliers (>*M* + 3.5 *SD*) *N* [%]
Intersections rate	472	0.09 (0.10)	0	1.32	6 [1.3%]
Best *r* (0-1)	472	.79 (.19)	.07	.99	1 [0.2%]
SC omission difference score (0-27)	472	1.22 (3.40)	0	26	12 [2.5%]
LB – average deviation (0-11°)	470	0.59 (0.91)	0	8.50	6 [1.3%]
CBS – total score (0-30)	405	4.54 (6.76)	0	30	4 [1.0%]
Balloons Test – laterality score (0-50%)	394	45% (9%)	0%	50%	10 [2.5%]
RCFT copy – total score (0-36)	293	28.90 (7.17)	5	36	0
TMT-A – duration in seconds	324	47 (26)	14	228	6 [1.9%]
TMT-B – duration in seconds	303	118 (63)	29	360	0
Tower Test – total score (0-30)	357	14.63 (4.06)	2	26	0
Brixton Test – number of errors	265	18.91 (7.46)	4	49	3 [1.1%]
DSF – longest sequence (2-10)	281	5.30 (1.11)	2	10	0
DSB – longest sequence (2-10)	281	3.89 (1.10)	2	9	0

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; LB, line bisection; RCFT, Rey Complex Figure Test; SC, shape cancellation test; TMT, Trail Making Test.

[1]Group sizes differ between measures since not all patients performed all neuropsychological tests. The minimum number of participants that performed a combination of two of the tests was 159 (for the Brixton Test and the RCFT).

Exploratory factor analyses

All patients

First, all variables correlated at least .3 with at least one other variable, suggesting reasonable factorability (Table 7.3). Furthermore, the Kaiser-Meyer-Olkin measure (KMO) was .76, thus, above the recommended value of .6, indicating that data were sufficient for exploratory factor analyses. The Barlett's test of sphericity, $\chi^2(78) = 432.82$, $p < .05$, showed that there were patterned relationships between the variables. The diagonals of the anti-image correlation matrix were all over .5, supporting the inclusion of each variable in the factor analysis. Using an eigenvalue cut-off of 1.0, there were four factors that explained a cumulative variance of 41.3%. We have labelled these factors as "Executive functioning" (i.e., TMT-A, TMT-B, Brixton Test, Tower Test), "Verbal memory" (i.e., DSF, DSB), "Search organization" (i.e., intersections rate, best r) and "Neglect" (i.e., CBS, RCFT copy, Balloons Test, SC omission difference score, LB). Table 7.4 shows the factor loadings after rotation using a significant factor criterion of .3. The factor Executive functioning correlated moderately with Verbal working memory, Search organization and Neglect. Furthermore, Search organization correlated moderately with Neglect. Small correlations were seen between Verbal working memory and Search organization, and Verbal working memory and Neglect.

Table 7.3 Correlation matrix of all measures (N = 439), Pearson correlation coefficients (r) are reported.

	Intersections rate	Best r	SC omission difference score	LB	CBS	Balloons Test	RCFT copy	TMT-A	TMT-B	Tower Test	Brixton Test	DSF
Best r	-.37	-										
SC omission difference score	.22	-.14	-									
LB	.05	-.14	.30	-								
CBS	.17	.02	.25	.17	-							
Balloons Test	-.24	.13	-.17	-.12	-.35	-						
RCFT copy	-.20	.25	-.23	-.25	-.35	.23	-					
TMT-A	.31	-.14	.29	.19	.19	-.29	-.36	-				
TMT-B	.22	-.09	.19	.13	.19	-.19	-.33	.72	-			
Tower Test	-.27	.11	-.14	-.08	-.18	.19	.35	-.41	-.46	-		
Brixton Test	.16	-.05	.11	.07	.08	-.19	-.33	.36	.39	-.29	-	
DSF	-.08	.04	-.18	-.04	.02	.00	.20	-.26	-.31	.23	-.15	-
DSB	-.13	.10	-.14	-.07	-.04	.07	.29	.30	-.40	.33	-.20	.48

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; LB, line bisection; RCFT, Rey Complex Figure Test; SC, shape cancellation test; TMT, Trail Making Test.

Table 7.4 Results of the exploratory factor analyses (*N* = 439).

Outcome	Factor				Communalities
	1. Executive functioning	2. Verbal working memory	3. Search organization	4. Neglect	
TMT-B	.88				.74
TMT-A	.81				.67
Brixton Test	.45				.22
Tower Test	-.43				.33
DSF		.66			.45
DSB		.64			.50
Best *r*			.83		.64
Intersections rate			-.39		.29
CBS				-.79	.55
RCFT copy				.42	.40
Balloons Test				.37	.25
SC omission difference score				-.37	.21
LB				-.32	.13
Eigenvalues	2.81	1.58	1.34	1.91	
% of variance	24.5	7.4	5.6	3.7	
Correlations between factors					
2. Verbal working memory	-.43				
3. Search organization	-.30	.18			
4. Neglect	-.48	.12	.33		

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; LB, line bisection; RCFT, Rey Complex Figure Test; SC, shape cancellation test; TMT, Trail Making Test.

Patients with right hemisphere damage

All variables correlated at least .3 with at least one other variable and the diagonals of the anti-image correlation matrix were all over .5. The KMO was .75 and he Barlett's test of sphericity was significant, $\chi^2(78) = 271.12$, $p < .05$. There were four factors that explained a cumulative variance of 44.5% (Table 7.5). The first factor was labelled as "Executive functioning/working memory" (i.e., TMT-A, TMT-B, DSB, DSF, Brixton Test, Tower

Table 7.5 Results of the exploratory factor analyses, including only patients with right-sided brain damage (*N* = 231).

Outcome	Factor				Communalities
	1. Executive functioning / working memory	2. Neglect / visual search	3. Search organization	4. Neglect	
TMT-B	.73	.32			.75
DSB	-.64				.41
TMT-A	.55	.34			.53
DSF	-.55				.28
Brixton Test	.50				.29
Tower Test	-.35				.36
CBS		.53		-.41	.55
Balloons Test		-.43			.27
Best *r*			.77		.62
Intersections rate		.45	-.48		.50
RCFT copy				.66	.68
LB				-.58	.32
SC omission difference score				-.43	.25
Eigenvalues	2.67	1.78	1.33	2.00	
% of variance	27.3	7.4	5.7	4.2	
Correlations between factors					
2. Neglect / visual search	.22				
3. Search organization	-.27	-.16			
4. Neglect	-.29	-.34	.22		

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; LB, line bisection; RCFT, Rey Complex Figure Test; SC, shape cancellation test; TMT, Trail Making Test.

Test). The second factor was labelled as "Neglect/visual search" (i.e., CBS, Balloons Test, intersections rate, and to a lesser extent, TMT-A, TMT-B). Finally, the factor "Search organization" (i.e., intersections rate, best *r*) and the factor "Neglect" (i.e., CBS, RCFT copy, LB, SC omission difference score) were obtained. The factors Neglect/visual search and Neglect showed moderate correlations, whereas the other factors showed small correlations between each other.

Patients with left hemisphere damage

The SC omission difference score, CBS, LB, and Balloons Test were removed from the model as they were not significant. All variables correlated at least .3 with at least one other variable and the diagonals of the anti-image correlation matrix were all over .5. The KMO was .63. The Barlett's test of sphericity was significant, $\chi^2(36) = 159.03$, $p < .05$. There were three factors that explained a cumulative variance of 46.8% (Table 7.6): "Executive functioning" (i.e., TMT-A, TMT-B, Brixton Test, RCFT copy, Tower Test), "Verbal memory" (i.e., DSB, DSB, Tower Test) and "Search organization" (i.e., intersections rate, best *r*). A moderate correlation was seen between Executive functioning and Verbal working memory, whereas the other factors showed small correlations.

Table 7.6 Results of the exploratory factor analyses, including only patients with left-sided brain damage (N = 208).

Outcome	Factor			Communalities
	1. Executive Functioning	2. Verbal working memory	3. Search organization	
TMT-A	-.88			.85
TMT-B	-.78			.70
Brixton Test	-.49			.21
RCFT copy	.33			.21
DSB		.86		.69
DSF		.64		.47
Tower Test	.36	.36		.37
Intersections rate			-.72	.53
Best *r*			.46	.21
Eigenvalues	2.33	1.85	.99	
% of variance	30.0	9.0	7.8	
Correlations between factors				
2. Verbal working memory	.40			
3. Search organization	.24	.19		

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; RCFT, Rey Complex Figure Test; TMT, Trail Making Test.

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Patients with high motor function

The RCFT copy was removed from the model as it was not significant. All variables correlated at least .3 with at least one other variable and the diagonals of the anti-image correlation matrix were all over .5. The KMO was .73. The Barlett's test of sphericity was significant, $\chi^2(66) = 236.70$, $p < .05$. There were four factors that explained a cumulative variance of 44.3% (Table 7.7): "Executive functioning" (i.e., TMT-B, TMT-A, Brixton Test, Tower Test), "Verbal working memory" (i.e., DSF, DSB, Tower Test), "Search organization" (i.e., best *r*, intersections rate), and "Neglect" (i.e., CBS, LB, Balloons Test, SC omission difference score). The factor Executive functioning showed moderate correlations with the other factors, whereas the correlations between the other factors was small.

Table 7.7 Results of the exploratory factor analyses, including only patients with no or little motor deficits in the arm (*N* = 223).

Outcome	Factor				Communalities
	1. Executive Functioning	2. Verbal working memory	3. Search organization	4. Neglect	
TMT-B	.80				.74
TMT-A	.79				.71
Brixton Test	.58				.30
DSF		.89			.45
DSB		.66			.77
Tower Test	-.31	.31			.30
Best *r*			.77		.55
Intersections rate			-.41		.33
CBS				-.64	.35
LB				.47	.24
Balloons Test				-.46	.30
SC omission difference score				-.41	.29
Eigenvalues	2.64	1.95	1.19	1.78	
% of variance	25.9	9.0	5.1	4.4	
Correlations between factors					
2. Verbal working memory	-.43				
3. Search organization	-.38	.10			
4. Neglect	-.47	.17	.27		

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; LB, line bisection; SC, shape cancellation test; TMT, Trail Making Test.

Discussion

The aim of the current study was to investigate associations between search organization during cancellation and other cognitive domains: neglect, visuospatial perception and construction, psychomotor speed, executive functioning, spatial planning, short-term auditory memory, and verbal working memory. To address this aim, we included 439 stroke patients and performed exploratory factor analyses. Our exploratory factor analysis revealed four key factors (eigenvalues >1.0; see Table 7.4). We have labelled these factors as “Executive functioning” (i.e., TMT-A, TMT-B, Brixton Test, Tower Test), “Verbal memory” (i.e., DSF, DSB), “Search organization” (i.e., intersections rate, best *r*) and “Neglect” (i.e., CBS, RCFT copy, Balloons Test, SC omission difference score, LB).

In our subsample of patients with right hemisphere damage, again, four factors summarized the underlying covariation (Table 7.5). The first factor consisted of several executive and verbal memory tests (i.e., TMT-A, TMT-B, DSB, DSF, Brixton Test, Tower Test). The second factor included a combination of neglect and visual search measures (i.e., CBS, Balloons Test, intersections rate, and to a lesser extent, TMT-A, TMT-B). Finally, the factor “Search organization” (i.e., intersections rate, best *r*) and the factor “Neglect” (i.e., CBS, RCFT copy, LB, SC omission difference score) were obtained. Measures of visual search (i.e., intersections rate, TMT-A, TMT-B) related with measures of neglect (i.e., CBS, Balloons Test), which is in line with prior findings (Rabuffetti et al., 2012; Ten Brink, Van der Stigchel, et al., 2016). Neglect and search organization seem different constructs, however, as search organization and neglect appeared to be separate domains as well in this sample.

For patients with left hemisphere damage, neglect variables were, not surprising, not significant, thus no “Neglect” factor was present (Table 7.6). The remaining three factors roughly compared with the main analyses: “Executive functioning” (i.e., TMT-A, TMT-B, Brixton Test, RCFT copy, Tower Test), “Verbal memory” (i.e., DSB, DSB, Tower Test) and “Search organization” (i.e., intersections rate, best *r*). This indicates that, although there is a positive relation between search organization and presence of neglect, search organization appears to be an important additional cognitive function next to existing functions that are measured during neuropsychological assessment. Overall, search organization measures constituted one separate cluster in all analyses.

We labelled the clusters based on the assumed shared functions of the measures within the cluster, yet most tests are sensitive to a number of different processes and could therefore belong to more than one cluster. The TMT, for example, measures search speed but is also considered to assess executive functioning. With respect to psychomotor speed, hemiparesis could have had a negative impact on the model. Limb weakness leads to impairment of both gross and fine motor skills and slows down motor responses. We, therefore, repeated our analysis in patients who were able to use their dominant hand and obtained high arm motor scores, and the results were largely comparable (Table 7.7).

With respect to short-term as well as working memory, the ‘sensory modality’ of the tests probably have had an influence on the lack of association with the search organization measures. Whereas search organization was measured with visuospatial tests, short-term and working memory were measured with verbal tests, but not their visuospatial counterparts. We did not have enough data of stroke patients on visuospatial short-term and working memory to also include these in our model.

Regarding the lack of association between search organization and higher-order spatial planning (such as applying spatial rules), test complexity might be a likely candidate for explanation. Several studies showed that the number of cancelled targets is affected by characteristics of the test. For example, less targets are cancelled when more targets are present (Chatterjee, Thompson, & Ricci, 1999) or with higher (non-spatial) cognitive demands (Ricci et al., 2016). Such factors might affect search organization too. Maybe even more relevant, are specific test instructions. In the current test, patients were not explicitly instructed to search in an organized manner or to search fast, and no specific order of cancellation was required to successfully complete the test (which is the case in the neuropsychological test that was used to assess higher-order spatial planning; the Tower Test). As a result, search organization during cancellation may be a relativeley automatic behaviour, which could explain the weak relationship with other cognitive domains. In future studies, it could be informative to study effects of different instructions on search organization, and how this changes the association with other tests. For example, planned organized search might relate more to other tests in which active planning is required, such as the Tower Task.

A recent lesion-symptom mapping study showed that stroke patients with less search organization had lesions in the right hemisphere, in particular, the temporoparietal junction (Ten Brink, Biesbroek, et al., 2016). These brain areas overlap with regions that have previously been associated with conjunctive search and spatial working memory (Humphreys & Chechlacz, 2015). Based on the involved brain areas (Ten Brink, Biesbroek, et al., 2016), and the behavioural results of the current neuropsychological study, we hypothesize that disorganized search is caused by disturbed spatial processes, rather than deficits in high-level executive function or planning. It should be noted, however, that these are speculations and more research is needed to test this hypothesis.

Finally, it must be stressed that, with the current exploratory factor analysis, we performed a first step to unravel the relation between search organization measures and other cognitive measures. Our main model explained 41.3% of the variance. This magnitude of explained variance can be considered as high and significant, given the heterogeneity of outcome measures and factors, capturing different aspects of the assumed underlying cognitive functions. Further research is needed to obtain a complete picture of the relation with search organization and other cognitive functions.

Limitations

A limitation of the current study is its retrospective nature. The choice of the neuropsychological tests for individual patients was based on the capacities of the patient, such as language or motor skills, and sometimes on the specific questions of the rehabilitation team. For example, patients with severe deficits in language production were not able to perform verbal memory tests. As a result, in the current sample, relatively little patients with left hemispherical damage were included, and, in general, the quality of communication was quite good.

The choices of the neuropsychological tests for the analyses were also restricted to the available data. The lack of associations between certain cognitive functions and search organization does not rule out the possibility that associations would have been found when other tests or outcome measures were used. Based on the literature, measures of, for example, spatial working memory, would have been important to include in our analyses. In most models of visual search, the implicit idea is that we remember where we have *looked* so that previously inspected locations are not returned to (Peterson, Kramer, Wang, Irwin, & McCarley, 2001). Both retrospective memory (i.e., keeping track of examined objects or locations) and prospective memory (i.e., strategic planning a series of shifts to specific objects) could, therefore, be involved in visual search (Peterson, Beck, & Vomela, 2007). Studies have shown that the relative contributions of different processes of visual search, such as spatial planning and working memory, vary across tests (e.g., based on test complexity) and individuals (e.g., stroke patients versus healthy subjects; Singh et al., 2017). Future, prospective, research should at least include visuospatial versions of memory tests for better comparison of the sensory modalities.

Additionally, several studies have examined eye movements during visual search tests to unravel underlying cognitive processes (e.g., Peterson et al., 2001; Shinoda et al., 2001). Measuring eye movements is thought to reflect visual search more directly compared to cancellation patterns, as one could have searched locations in a different order than the order the targets were eventually cancelled. In a small study (i.e., 16 stroke patients), however, it was found that the number of saccades and the degree of search organization based on motor responses (i.e., in a TMT task) were negatively related with each other (Singh et al., 2017). This indicates that measuring eye movements during visual search could yield comparable results compared to measuring cancellation patterns during visual search. On the other hand, the seemingly obvious relation between eye movements and attention could be disturbed after brain damage. In a case study with a patient suffering from optic ataxia, this patients' fixation did not directly imply attention for the fixated goal (Khan et al., 2009). This could indicate that evaluating the pattern of *cancelled* targets might, therefore, be a proper measure for visual search in a *clinical setting* with a heterogeneous patient population. Currently, however, no studies with large enough cohorts of stroke patients have been performed regarding the relation between eye movements and attention. It is, therefore, unclear which measure would best reflect aspects of visual search. Future studies could target the direct associations between eye movements and search organization derived from behavioural measures, by using eye tracking during visual search tasks (such as cancellation or TMT).

One of the other issues in this study could have been the problem of "method variance". Method variance means that measures extracted from the same test will have larger associations, as the same stimuli are used (Yong & Pearce, 2013). However, the SC omission difference score and the measures of search (all derived from the same test) were not in the same cluster, suggesting that the problem of method variance at least did not cause all results. In addition, tests were administered in two different sessions with a variable time window of 1 to 14 days. Given that recovery (spontaneous or due to training) takes place in this particular phase post-stroke onset, patients with a longer time window in between sessions might have had better scores on the second session compared to the first one. This could have influenced the association between the search variables and other neuropsychological clusters. If anything, however, the association between the search variables and the cognitive measures that were administered within the same session (i.e., the neglect measures) would then potentially be stronger, which we did not observe.

Finally, some potentially relevant information was not, or insufficiently, available, such as information on stroke territories or visual field defects. The presence of a visual field defect could contribute to disturbed visuospatial perception and visual search. Excluding patients with occipital lesions or visual field defects, however, would lead to the loss of an important patient group, as patients with posterior damage often show neglect and would then be underrepresented in the sample (Mort, 2003). In addition, pure visual input failure does not fully account for disorganized search (Behrmann, Ebert, & Black, 2004; Machner, Sprenger, Kömpf, et al., 2009; Machner, Sprenger, Sander, et al., 2009).

Conclusion and implications

To summarize, the results of the exploratory factorial analyses show that measures of search organization constitute one cognitive cluster of their own, next to “Executive functioning”, “Verbal memory” and “Neglect”. Measuring search organization during cancellation may provide useful additional insights into the visuospatial processes and attention of stroke patients, the change over time, or the effects of a given treatment. Possibly, patients with disorganized search could experience negative consequences in ADL. Importantly, measures of search organization can easily being extracted during assessment of computerized cancellation tests (Dalmaijer et al., 2014; Donnelly et al., 1999; Huang & Wang, 2008). Future research needs to examine what the consequences of disorganized search are in daily life, whether search organization can be trained during rehabilitation, for example with prism adaptation (De Wit, Ten Brink, Visser-Meily, & Nijboer, 2016), and whether training generalizes to daily life.

Acknowledgements

This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN, and the “Revalidatiefonds” under grant R2012134 to TCWN and JMAVM.

Supplementary Table 1. **Clinical characteristics at admission to rehabilitation, median scores (IQR) or frequencies [%], for the three different subgroups (i.e., patients with right-sided brain damage, left-sided brain damage, high motor scores; all without outliers)**

	Right-sided brain damage		Left-sided brain damage		High motor scores	
Outcome	*N*[1]	*Mdn* (IQR) or *N* [%]	*N*[1]	*Mdn* (IQR) or *N* [%]	*N*[1]	*Mdn* (IQR) or *N* [%]
Age, in years	231	61 (17)	208	60 (14)	223	61 (14)
Sex, % male	231		208		223	
- Male		132 [57%]		131 [63%]		126 [57%]
- Female		99 [43%]		77 [47%]		97 [44%]
Level of education (1-7)	231	5 (2)	208	5 (2)	223	5 (2)
Days post-stroke[2]	231	22 (15)	208	21 (11)	223	20 (12)
Delay between neglect screening and neuropsychological assessment	231		208		223	
- ≤ 1 week		150 [65%]		150 [72%]		155 [70%]
- > 1 week		81 [35%]		58 [28%]		68 [31%]
Aetiology	231		208		223	
- Ischemic		179 [78%]		147 [71%]		171 [77%]
- Intracerebral haemorrhage		40 [17%]		55 [26%]		41 [18%]
- Subarachnoid haemorrhage		12 [5%]		6 [3%]		11 [5%]
Lesion side	231		208		223	
- Left		0		208 [100%]		119 [53%]
- Right		231 [100%]		0		104 [47%]
Stroke history	231		208		223	
- First		157 [68%]		145 [70%]		175 [78%]
- Recurrent		24 [10%]		17 [8%]		24 [11%]
- Unknown		60 [22%]		46 [22%]		24 [11%]
MoCA (0-30)	180	23 (2)	132	22 (6)	191	22 (5)
SAN (1-7)	181	7 (1)	167	5 (3)	213	6 (2)
Motricity Index arm (0-100)	176	76 (61)	171	78 (39)	223	100 (24)
Motricity Index leg (0-100)	175	76 (41)	169	83 (43)	220	99 (25)
Barthel Index (0-20)	176	13 (8)	160	16 (9)	201	17 (7)

Abbreviations: MoCA, Montreal Cognitive Assessment; SAN, Stichting Afasie Nederland.

[1]Group sizes differ since not all clinical data was available for all patients.

[2]Days post-stroke at the time of the neglect screening.

Supplementary Table 2. **Mean scores and standard deviations on visual search measures and neuropsychological tests, for the three different subgroups (i.e., patients with right-sided brain damage, left-sided brain damage, high motor scores; all without outliers)**

	Right-sided brain damage		Left-sided brain damage		High motor scores	
Outcome	*N*[1]	*M* (*SD*)	*N*[1]	*M* (*SD*)	*N*[1]	*M* (*SD*)
Intersections rate	231	0.09 (0.10)	208	0.07 (0.08)	223	0.08 (0.09)
Best *r*	231	.78 (.20)	208	.83 (.17)	223	.79 (.20)
SC omission difference score	231	0.74 (1.50)	208	0.49 (1.30)	223	0.65 (1.41)
LB – average deviation	230	0.47 (0.48)	207	0.45 (0.42)	223	0.48 (0.45)
CBS – total score	191	4.96 (6.92)	184	2.63 (4.20)	195	2.72 (4.75)
Balloons Test – laterality score	184	45% (6%)	182	48% (3%)	186	47% (5%)
RCFT copy – total score	144	29.04 (6.30)	124	30.97 (5.90)	142	30.09 (6.44)
TMT-A - duration in seconds	183	53 (25)	125	49 (23)	155	51 (25)
TMT-B - duration in seconds	178	129 (66)	112	140 (83)	148	135 (75)
Tower Test – total score	174	14.52 (4.19)	166	14.66 (4.49)	167	15.01 (4.39)
Brixton Test – number of errors	131	18.75 (7.05)	126	18.16 (6.54)	127	18.09 (7.19)
DSF – longest sequence	157	5.32 (1.09)	101	5.27 (1.13)	126	5.17 (1.09)
DSB – longest sequence	157	3.92 (1.10)	101	3.90 (1.07)	126	3.89 (1.19)

Abbreviations: CBS, Catherine Bergego Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; LB, line bisection; RCFT, Rey Complex Figure Test; SC, shape cancellation test; TMT, Trail Making Test.

[1]Group sizes differ between measures since not all patients performed all neuropsychological tests.

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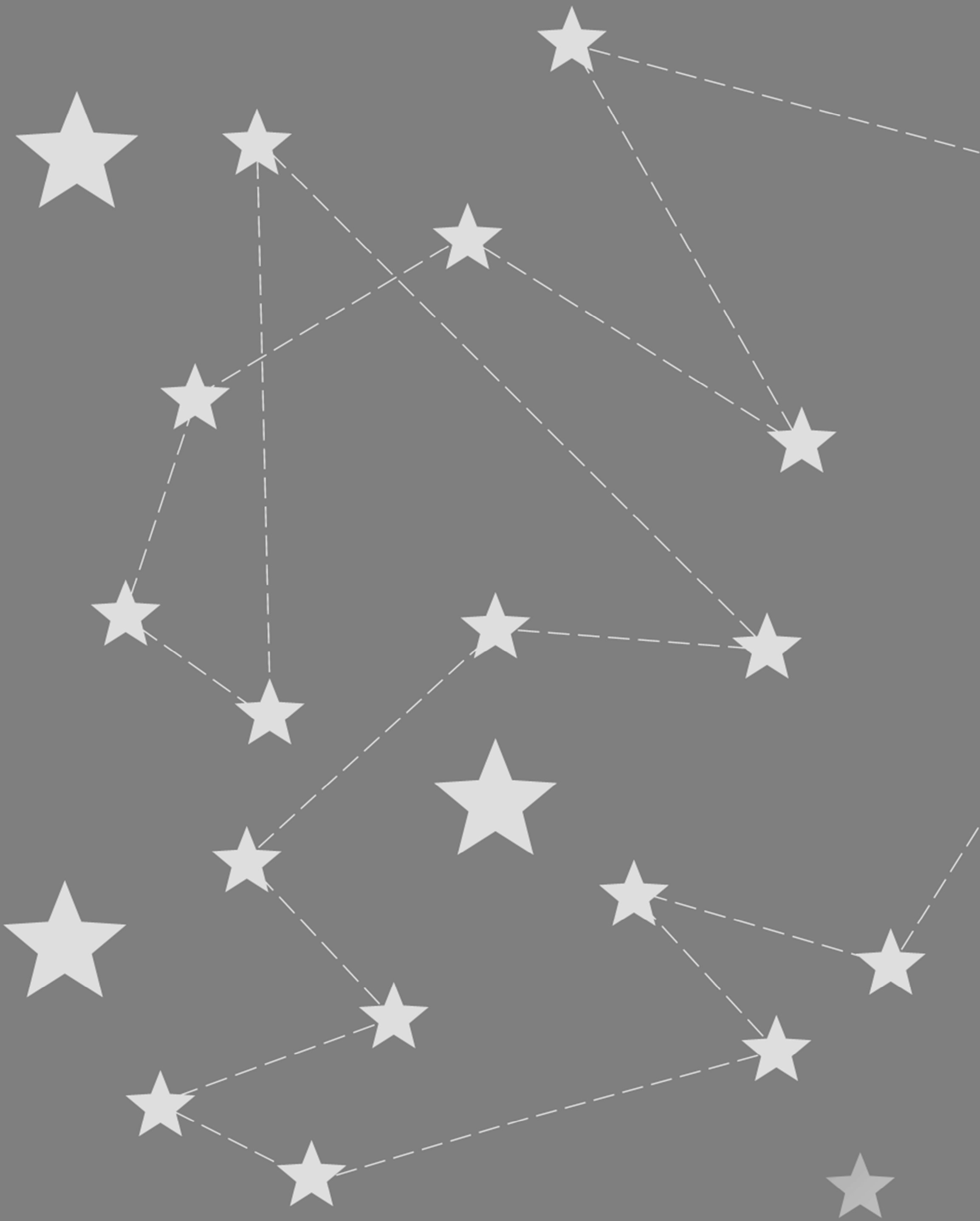

Part III

Prism adaptation in the rehabilitation of neglect

Chapter 8

Does prism adaptation affect visual search in spatial neglect patients: A systematic review

De Wit, L*, Ten Brink, A. F.*, Visser-Meily, J. M. A., Nijboer, T. C. W. (In press). Does prism adaptation affect visual search in spatial neglect patients: A systematic review. *Journal of Neuropsychology*.

** The first two authors contributed equally to this work.*

Abstract

Prism adaptation (PA) is a widely used intervention for (visuo)spatial neglect. PA-induced improvements can be assessed by visual search tasks. It remains unclear which outcome measures are the most sensitive for the effects of PA in neglect. In this review, we aimed to evaluate PA effects on visual search measures. A systematic literature search was completed regarding PA intervention studies focusing on patients with neglect using visual search tasks. Information about study content and effectiveness was extracted. Out of 403 identified studies, 30 met the inclusion criteria. The quality of the studies was evaluated: rankings were moderate-to-high for 7, and low for 23 studies. As feature search was only performed by five studies, low-to-moderate ranking, we were limited in drawing firm conclusions about the effect of PA on feature search. All moderate-to-high ranking studies investigated cancellation by measuring only omissions or hits. These studies found an overall improvement after PA. Measuring perseverations and total task duration provides more specific information about visual search. The two (low ranking) studies that measured this, found an improvement after PA on perseverations and duration (while accuracy improved for one study and remained the same for the other). This review suggests there is an overall effect of PA on visual search, although complex visual search tasks and specific visual search measures are lacking. Suggestions for search measures that give insight in subcomponents of visual search are provided for future studies, such as perseverations, search path intersections, search consistency and using a speed-accuracy trade-off.

Introduction

Unilateral visuospatial neglect ("neglect") is a common disorder after a stroke (Nijboer, van de Port, et al., 2013). It is defined as an attentional failure to report, respond to, or orient to stimuli presented in the contralesional hemispace, not caused by motor or sensory deficits (Heilman & Watson, 1977). Neglect is a complex, multicomponent disorder, including not only the abovementioned spatially lateralized, but also non-lateralized (e.g., spatial working memory) deficits (Husain & Rorden, 2003). It is associated with a lower functional (i.e., activities in daily living) recovery from stroke (Nijboer, van de Port, et al., 2013). In 40% of patients, neglect becomes chronic and is still present 1 year post-stroke onset (Nijboer, Kollen, et al., 2013).

A promising method for the rehabilitation of neglect is prism adaptation (PA), first applied by Rossetti et al. (1998) and widely used ever since. Reduction of neglect symptoms can last for a short period of time after a single PA session (e.g., 2 hr; Rossetti et al., 1998) and for a long period of time after multiple sessions (up to 24 months after 3 months of daily sessions; Nijboer, Nys, van der Smagt, van der Stigchel, & Dijkerman, 2011). Although symptom reductions have been reported in various domains, not all symptoms improve. The underlying (neural) mechanisms of the interaction between PA and specific aspects of neglect remain unclear (Newport & Schenk, 2012).

Most studies looked into the effects of PA on tasks using visual stimuli. These tasks typically involve actively scanning a visual environment for targets among distractors, in which often visuo-motor responses are assessed. Patients with neglect generally have problems with visual search and achieving proper visual overview (Ten Brink, Van der Stigchel, et al., 2016), which can result in a disorganized search pattern during cancellation tasks. Spatial working memory also plays a crucial role in visual search and is considered to be an important component of the neglect syndrome (Husain et al., 2001; Malhotra, Mannan, Driver, & Husain, 2004). Eye tracking research has indicated that patients with neglect tend to re-fixate, and re-examine previously examined targets more than healthy controls, showing an inability to keep track of previously examined targets (Husain et al., 2001; Malhotra et al., 2004) as would be seen in spatial working memory deficits.

The effects of PA on visual search might depend on the procedure of PA (Jacquin-Courtois et al., 2013). Two main procedures can be distinguished: either the second half and final part (including the pointing error) of the pointing movement are visible (i.e., concurrent feedback) or only the final part (i.e., terminal feedback). Làdavas, Bonifazi, Catena, and Serino (2011) compared these procedures and found greater effects after terminal feedback, which they explained in terms of a correction of visuo-motor eye-hand coordinates when using terminal feedback, whereas the concurrent feedback procedure causes a correction of proprioceptive coordinates.

It is unknown which sub processes of visual search are affected by PA in patients with neglect. There is debate in the literature about whether PA affects the dysfunction in the attentional and visuo-motor circuits in the dorsal visual stream (e.g., Fortis, Chen, Goedert, & Barrett, 2011; Striemer & Danckert, 2010) and/or in the explicit perceptual judgments circuits in the ventral stream (e.g., Serino, Bonifazi, Pierfederici, & Làdavas, 2007). However, there is evidence that the orienting of attention (e.g., Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003) and exploratory motor behaviours (e.g., Dijkerman et al., 2003; Striemer & Danckert, 2007) are influenced after PA, whereas perceptual judgements (e.g., estimating shape size and judging chimeric faces) are unaffected (Dijkerman et al., 2003; Striemer & Danckert, 2007).

Improvements of rehabilitation techniques for neglect are commonly evaluated using cancellation and other visual search tasks. It remains unclear which visual search outcome measures are the most sensitive for the beneficial effects of PA. We aim to evaluate effects of PA on various visual search measures. This can help us understand which measures, and which aspects of visual search, are ameliorated by PA.

Methods

Search methods and article selection

A literature search was performed using PubMed and Scopus for studies published up until January 2015. Three searches were performed. First, we searched for “neglect” combined with “PA”. Second, we searched for “stroke or cerebrovascular disease” combined with “PA”. Last, to be more specific, we searched for “visual search or search accuracy or search efficiency or search strategy or cancellation or BIT or behavioural inattention test” combined with “PA”. The majority of studies were found after the first two searches. Studies were selected if they met the following inclusion criteria: (1) stroke patients with neglect; (2) ≥18 years of age; (3) measures of visual search (cancellation tasks or other types of visual search tasks); (4) a PA intervention; and (5) at least two visual search measurements (pre-PA and post-PA). Non-English studies, review papers, and book chapters were excluded. Subsequently, duplicates were excluded. Two authors (LDW and AFTB) screened the titles and abstracts. From screen-positive titles and abstracts or in case of ambiguity, full-text articles were collected and evaluated with the aforesaid criteria.

Data extraction

LDW and AFTB extracted the following characteristics from the articles: aim, design, number of patients, mean age, side of neglect, time post-stroke onset, duration and intensity of treatment sessions, PA procedure, deviation of prism goggles, alternative intervention, timing of measurements, type of visual search tasks, outcome measures, and results (i.e., differences between pre- and post-measurements or between treatment and control group).

Quality assessment

LDW and AFTB independently appraised the characteristics and the quality of the studies. The methodological quality was evaluated based on elements from Tijssen and Assendelft (2003): (1) comparison of an experimental group and a control group; (2) randomization of conditions; (3) comparability of groups at the start of the study; (4) equal treatment of groups (excluding intervention); (5) blinding of effect evaluators; and (6) reporting completeness of follow-up (follow-up measurements were defined as ≥3 months post-treatment). Two criteria were added: (7) reporting time post-stroke, as this might affect the efficacy of PA; and (8) reporting effect size, as this is informative about the magnitude of the intervention effect.

The criterion “blinding of the practitioner” and “blinding of participants” of Tijssen and Assendelft (2003) were not applied, as the prism goggles provide information about the experimental condition. In case a criterion was not applicable, 0 points were assigned. This checklist yielded a total score ranging between 0 and 8. Studies were labelled as high (total scores ≥6), moderate (4 and 5), or low (≤3) ranking.

Results

In the initial search, 402 articles were identified, of which 30 were included (Figure 8.1). The selected articles yielded an inter-rater reliability of 98.1%, with an agreement of 100% after discussion. The specifics of the selected studies are presented in Table 8.1.

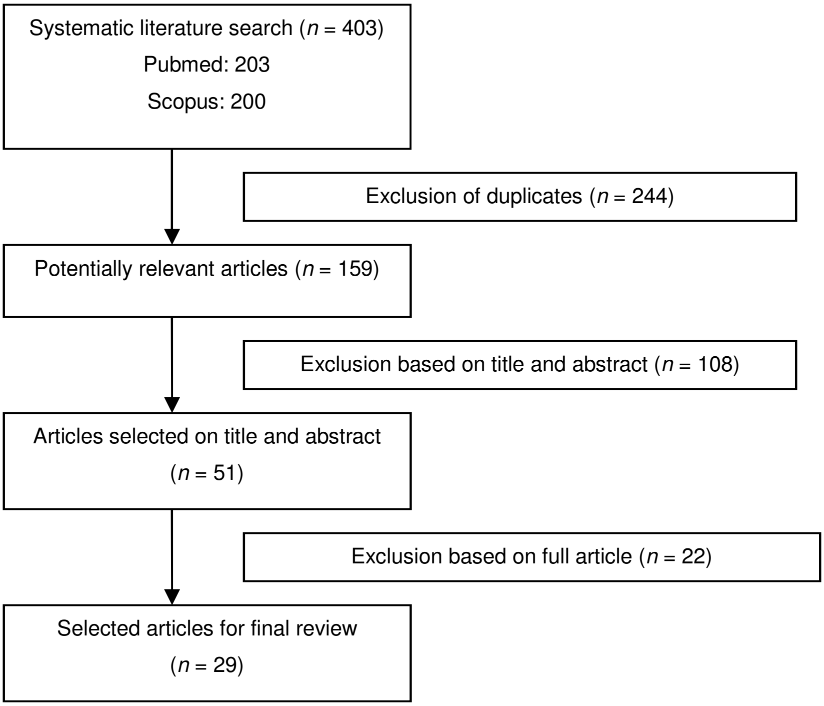

Figure 8.1 Flowchart of article selection

Quality assessment

The quality assessment yielded an inter-rater reliability of 96.3%, with an agreement of 100% after discussion with TCWN. The studies of Serino, Barbiani, Rinaldesi, and Ladavas (2009) and Priftis, Passarini, Pilosio, Meneghello, and Pitteri (2013) were ranked as high (Table 8.2). The studies of Mancuso et al. (2012), Nys, de Haan, Kunneman, de Kort, and Dijkerman (2008), Rossetti et al. (1998), Vangkilde and Habekost (2010), and Saevarsson, Kristjansson, and Halsband (2010) were ranked as moderate. All other studies (n = 23) were ranked as low (Table 8.2).

Study, intervention, and patient characteristics

Study characteristics

There were eight randomized controlled trials, four studies with a crossover design, and 18 studies with a pre-post design (12 studies testing a group of participants, five case studies, and one pilot study without reporting statistical analyses).

Intervention characteristics

There is no standard protocol for PA treatment. Most studies used 10º prism goggles, with the exception of Mancuso et al. (2012; 5º), Morris et al. (2004; 15º), Shiraishi, Muraki, Ayaka Itou, and Hirayama (2010; 15º), and Saj, Cojan, Vocat, Luauté, and Vuilleumier (2013; 20º). Visual targets were located at 10° to 25° from the midline, with or without a central target. Keller, Lefin-Rank, Lösch, and Kerkhoff (2009) only used one central target. In one study, targets were pointed at with a digital stylus (Smit et al., 2013). In all other studies, participants used their finger. The number of pointing movements ranged from 8 to 20 (Keller et al., 2009), up to 200 (Morris et al., 2004) per session. Moreover, Fortis et al. (2010) compared the classic pointing procedure (Rossetti et al., 1998) with a new method in which prismatic goggles had to be worn while performing ecologically valid activities.

The view of the pointing movement was obstructed in most studies, by either holding a board above the patients arm or using an adaptation box. The terminal feedback procedure was used in 12 studies (Eramudugolla, Boyce, Irvine, & Mattingley, 2010; Fortis et al., 2010; Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Mancuso et al., 2012; McIntosh, Rossetti, & Milner, 2002; Priftis et al., 2013; Rusconi & Carelli, 2012; Saevarsson et al., 2010; Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009; Serino et al., 2007, 2009; Vangkilde & Habekost, 2010). Eleven of these found (some) significant effects of PA. Twelve studies used the concurrent feedback procedure (Farnè, Rossetti, Toniolo, & Ladavas, 2002; Gossmann et al., 2013; Jacquin-Courtois et al., 2008; Keane, Turner, Sherrington, & Beard, 2006; Luauté et al., 2012; Morris et al., 2004; Nijboer et al., 2011; Nys, de Haan, et al., 2008; Nys, Seurinck, & Dijkerman, 2008; Rossetti et al., 1998; Rousseaux, Bernati, Saj, & Kozlowski, 2006; Sarri et al., 2008) of which nine found (some) significant effects of PA. In several studies the obstruction procedure was not clearly described (Humphreys, Watelet, & Riddoch, 2006; Keller et al., 2009; Saj et al., 2013; Shiraishi et al., 2010; Smit et al., 2013; Vallar, Zilli, Gandola, & Bottini, 2006).

None of the studies explicitly described blinding of the effect evaluators.

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Table 8.1 The extracted information from the discussed studies

Study	Design	*N* patients (exp. + control)	Time post-stroke	*N* sessions (wk) and PA procedure	Alter-native inter-vention	Times of measure-ment	Visual search task	Visual search outcome measures	*p*-values and effect sizes	Ranking
Serino et al. (2009)	RCT	10 + 10	1-60 m	10 (2) Terminal	SA	Pre, PA/SA, post (2 and 4 wk)	Bell+Star+ Letter[a]	%Hits left side	Session: $p < .0003$, $\eta = .77$ *Post-hoc*: PA in comparison with other treatments: $p < .008$	High
Priftis et al. (2013)	RCT	11 + 10 + 10	31-223 d	20 (2) Terminal	Visual scanning training; limb activation treatment	Pre (2x), PA, post (direct, 2 wk)	Picture scanning Room description	Hits	Session: $p < .001$, $\eta_p^2 = .209$ (pre2-post [direct]: $p < .05$) Intervention type*session: NS Session: NS (pre2-post [direct]: NS) Intervention type*session: NS	High
Rossetti et al. (1998)	RCT	6 + 6	3 wk-14 m	1 Concurrent	SA	Pre, PA/SA, post (direct, 2 h)	Line	Omissions per half	Group*session: $p < .05$ Pre-post [direct]: $p < .01$ Pre-post [2 h]: $p < .01$ Post [direct]-post [2 h]: $p > .95$	Moderate
Nys, de Haan, et al. (2008)	RCT	10 + 6	2-23 d	4 (1) Concurrent	SA	For every session: pre, PA/SA, post (direct, 1 m)	Letter Star	Hits Hits	Session: NS; group*session: $p = .045$ Session: $p < .001$ Pre-post [1 m]: NS	Moderate
Vangkilde and Habekost (2010)	RCT	6 + 5	6-138 m	20 (2) Terminal	General cognitive rehabilitation	Pre, PA, post (1-2 d, 5 wk)	Cupboard test Mesulam star Mesulam letter Where is Wally	Omdiff Time Omdiff Omdiff Omdiff RT	$p = .033$, $\eta_p^2 = .32$ $p = .001$, $\eta_p^2 = .52$ $p = .001$, $\eta_p^2 = .56$ $p = .003$, $\eta_p^2 = .48$ $p = .047$, $\eta_p^2 = .29$ $p = .003$, $\eta_p^2 = .32$ *N.B. All of these results are group*session interaction effects*	Moderate
Mancuso et al. (2012)	RCT	13 + 9	20-1140 d	5 (1) Terminal	SA	Pre, PA/SA, post	Bell Object	%Hits left side %Hits right side %Hits left side %Hits centre %Hits right side	Session: $p = .009$; group*session: $p = .508$ Session: $p = .148$; group*session: $p = .011$ Session: $p = .015$; group*session: $p = .824$ Session: $p = .724$; group*session: $p = .035$ Session: $p = .164$; group*session: $p = .732$	Moderate

Saevarsson et al. (2010)	RCT	6 NVPA + 6 NV	3-57 m	1 Terminal	NV without PA	Pre, PA, post (1 d)		*Between groups:*		Moderate
							Pop-out task	RT	Treatment*session: $p > .4$(NS)	
								%Hits	Treatment*session: $p > .2$(NS)	
							Albert's+Digit +Star+Letter[a]	RT	Treatment*session: $p = .018$[b]	
								%Hits	Treatment*session: $p = .037$	
								Within PA group:		
							Pop-out task	Target absent pop-out RT	$p < .001$ *(slower responses!)*	
								Target present pop-out RT	$p < .001$	
								Target absent pop-out %Hits	NS	
								Target present pop-out %Hits	$p < .001$	
							Albert's+Digit+ Star+Letter[a]	RT	NS	
								%Hits	$p = .089$ (NS)	
Frassinetti et al. (2002)	RCT	7 + 6	3-27 m	20 (2) Terminal	None	Pre, PA, post (2 d, 1 and 5 wk)	Line+Letter+ Star+Bell[a]	%Hits *transformed in arcsine values*	Side*session: $p < .0007$ Session: $p < .00001$ (pre-post [2 d]: $p < .0007$; pre-post [1 wk]: $p < .0002$; pre-post [5 wk]: $p < .0002$) Control group, session: NS *N.B. Only the scores of the total search array are reported. The same analyses were done for the left side (significant) and the right side (NS)*	Low
Fortis et al. (2010)	Cross-over	10 Follow-up: 4/10	3.4 m	10 (1) CPA Terminal + 10 (1) EPA	CPA	Pre (3x), CPA/EPA, post (direct, 0.5 and 1wk) CPA/EPA, post (direct, 1.5 wk, 1 and 2 m), follow-up: (3 m) *(counterbalanced)*	Letter Bell Star	%Hits %Hits %Hits	Session*group: $p = .40$ Session*group: $p < .05$ Session*group: $p = .11$ *Follow-up (average of 3 measurements):* Post [direct2]-post [1 m]: $p = .19$, $\eta p^2 = .26$ Post [1 m]-post [2 m]-post [3 m]: $p = .58$, $\eta p^2 .16$ *N.B. Not tested in comparison to baseline*	Low

Table 8.1 (continued)

Study	Design	*N* patients (exp. + control)	Time post-stroke	*N* sessions (wk) and PA procedure	Alter-native inter-vention	Times of measure-ment	Visual search task	Visual search outcome measures	*p*-values and effect sizes	Ranking
Serino et al. (2007)	One group pre and post	21 Follow-up (6 m): 9/21	3-96 m	10 (2) Terminal	NA	Pre, PA, post (direct, 1 wk, 1 m), follow-up (3 and 6 m)	Bell+Letter+ Star[a]	%Hits	*Left side:* Pre-post [direct]: $p = .0002$ Pre-post [1wk]: $p = .0002$ Pre-post [1m]: $p = .0002$ *Right side*: Pre-post [direct]: $p = .003$ Pre-post [1wk]: $p = .0009$ Pre-post [1m]: $p = .002$ *Follow-up:* side*session: $p = .002$ Pre-post [direct]: $p = .02$ Pre-post [1wk]: $p = .0002$ Pre-post [1m]: $p = .0002$ Pre-post [3m]: $p = .0002$ Pre-post [5m]: $p = .0002$	Low
Eramudugolla et al. (2010)	One group pre and post	12	1-15 m	2 (1-2) Terminal	NA	Pre (2x), PA1, post (direct), PA2, post (direct)	Balloons	Hits left vs. right side task A Hits left vs. right side task B	All measures: session: $p > .10$ Target location*session: $p > .10$ All measures: session: $p < .05$, $\eta_p^2 = .27$ Target location*session: $p = .05$, $\eta_p^2 = .23$	Low
Shiraishi et al. (2010)	One group pre and post	5 Follow-up: 5/7	14-84 m	±24 (8) Procedure unclear	NA	Follow-up (of study 2-3.5 y earlier)	Letter Star	Omissions left side Omissions left side	$p < .05$ $p = .104$ (NS)	Low
Nijboer et al. (2011)	Case study	1	70 m	Daily for 3 months Concurrent	NA	Pre, PA, post (3 m after start), follow-up (3, 6, and 24 m after final PA session)	Star	Omissions Perseverations Duration	Session: $p = .008$ Session: $p = .001$ Session: $p < .001$	Low
Rusconi and Carelli (2012)	One group pre and post	7 Follow-up: 7/7	2-6 m	20 (2) Terminal	NA	Pre, PA, post (2 wk), follow-up (8-30 m)	Line Letter Star	BIT scores BIT scores BIT scores	Pre-post [2 wk]: NS Pre-follow-up: NS Pre-post [2 wk]: NS Pre-follow-up: NS Pre-post [2 wk]: significant, *p*-value unclear Pre-follow-up: $p < .05$	Low

Farnè et al. (2002)	One group pre and post	6	2-8 m	1 Concurrent	NA	Pre, PA, post (direct, 1 d, 1 wk), PA2, post (direct)	Line Bell Letter	%Hits %Hits %Hits *N.B. The percentages of hits were transformed in arcsine values*	For all tests: Pre-post [direct]: $p < .05$ Pre-post [1 d]: $p < .05$ Pre-post [1 wk]: NS	Low
McIntosh et al. (2002)	Case study	1	9 m	3 (3) Terminal	NA	Pre (2x), PA, post (direct), pre, PA2, post (2 h), pre, A3, post (direct)	Star	Omissions per half	Pre-post: $p < .001$ (a*ll pre and post data were pooled)* Week: $p < .001$ *(all data were pooled per week)*	Low
Morris et al. (2004)	One group pre and post	First task: 4 Second task: 3	1-6 m	1 Concurrent	NA	SA, pre, PA, post (direct)	Unique feature search	RT	*Pre-post:* For 2/4 patients: $p < .01$ For 2/4 patients: NS *Interaction horizontal target location-adaptation:* For 3/4 patients: $p > .10$ For 1/4 patients: $p = .066$	Low
							Absent feature search	RT	*Pre-post:* For 3/3 patients: $p > .05$ (NS) *Interaction horizontal target*[c] *location-adaptation:* For 1/3 patients: $p < .05$ For 2/3 patients: $p > .10$	
Humphreys et al. (2006)	Case study	1	11 y	10 (5) + 8 (4) Procedure unclear	NA	Pre (2x), PA1, post (direct 2x, 1 m), PA2, post (1 wk, 5 wk)	Star Letter	Omissions Omissions	Pre-post after PA1: $p < .05$ Pre-post after PA2: $p < .01$ Pre post after PA1: $p < .01$ Pre-post after PA2: $p < .01$	Low
Rousseaux et al. (2006)	Cross-over	10	17-102 d	1 Concurrent	SA	Pre (2x), PA/SA, post (direct, 3 h, 1 and 3 d); after 1 wk break alternative treatment (same times)	Bell	Omdiff	NS	Low

Table 8.1 (continued)

Study	Design	*N* patients (exp. + control)	Time post-stroke	*N* sessions (wk) and PA procedure	Alter-native inter-vention	Times of measure-ment	Visual search task	Visual search outcome measures	*p*-values and effect sizes	Ranking
Vallar et al. (2006)	One group pre and post	9	2-36 d	1 Procedure unclear	NA	Pre, PA, post (direct, 60 min)	Line	Omissions Perseveration errors	Session: $p < .05$ (pre-post [direct]: $p < .05$; pre-post [60 min]: $p < .05$) Session: $p < .05$ (pre-post [direct]: $p < .05$; pre-post [60 min]: $p < .05$)	Low
Nys, Seurinck, et al. (2008)	Case study	1	11 m	4 (1) Concurrent	NA	For every session: pre, PA, post (direct)	Star	%Hits left %Hits right %Perseverations left %Perseverations right	$p < .01$ NS $p < .01$ $p < .01$	Low
Sarri et al. (2008)	One group pre and post	12[c]	1-174 m	1 Concurrent	NA	Pre, PA, post (direct)	Mesulam shape	%Hits	For 7/12 patients significant: $p < .001$, $p < .001$, $p < .05$, $p < .05$, $p < .001$, $p < .001$, $p < .05$ For 5/12 patients: NS	Low
Keller et al. (2009)	Cross-over	10	2-4.5 m	1 Procedure unclear	OKSP; visual scanning; OKSP + arm movements; OKSP + PA	For every treatment: pre, treatment, post(direct), 1 wk break; subsequently alternative treatments (same times) *(counterbalanced)*	Cancellation (not further specified)	Omissions	$p = .045$	Low
Saevarsson et al. (2009)	One group pre and post	Exp. 1: 4 Exp. 2: 4	3-61 m	1 Terminal	NA	Pre (20 d before PA), PA, post (direct)	Pop-out search task[d]	Exp. 1: RT left Exp. 1: RT right Exp. 1: RT target absent Exp. 1: %Hits Exp. 2: RT left Exp. 2: RT right Exp. 2: RT target absent	$p < .001$ $p < .001$ $p < .001$ (*significantly slower!*) NS $p < .001$ $p < .001$ $p < .001$	Low

								Exp. 2: %Hits left Exp. 2: %Hits right Exp. 2: %Hits target absent	$p < .001$ $p < .001$ NS	Low
Luauté et al. (2012)	One group pre and post	5	1-2.5 m	1 Concurrent	NA	Pre, PA, post (direct, 2 h)	Line Balloon pop-out Balloon search	Hits Hits Hits	$p = .32$ (NS) $p = .46$ (NS) $p = .98$ (NS)	Low
Gossmann et al. (2013)	One group pre and post	16	36 d	4 (1) Concurrent	NA	Pre (2x), PA, post (5-6 d, 10-12 d)	Apples	Hits	Pre-post [5-6 d]: $p = .041$ Pre-post [10-12 d]: $p = .006$	Low
Saj et al. (2013)	One group pre and post	7	10-32 d	1 Procedure unclear	NA	Pre (2x), PA, post (direct)	Visual search of single-odd item	RT %Hits %Hits	NS Pre1-post [direct]: $p = .005$ Pre2-post [direct]: $p = .008$	Low
Smit et al. (2013)	One group pre and post	33	63.73 d	1 Procedure unclear	NA	Pre, PA, post (direct)	Object	Omissions Time Search time ipsilateral Search time contralateral Center of cancellation	NS $p = .003$ $p = .0001$ $p = .004$ NS	Low
							Letter	Omissions Time Search time ipsilateral Search time contralateral Center of cancellation	NS $p = .025$ NS $p = .027$ NS	
Keane et al. (2006)	Pilot	4	<60 d	5 (12-17 d) Concurrent	NA	Albert's line: for every session pre, PA, post Letter: pre, PA (entire treatment), post	Line Letter	Errors Errors *N.B. Errors most likely equals omissions, but this is not explicit*	No statistical analyses were done. The non-statistical results are not discussed in the text.	Low

Table 8.1 (continued)

Study	Design	*N* patients (exp. + control)	Time post-stroke	*N* sessions (wk) and PA procedure	Alter-native inter-vention	Times of measure-ment	Visual search task	Visual search outcome measures	*p*-values and effect sizes	Ranking
Jacquin-Courtois et al. (2008)	Case study	1	3 or 5 m	1 Concurrent	NA	Pre (3x), PA, post (direct, 1, 24, 48, 72, and 96 h)	Line	Omissions	Pre-overall post: $p < .05$ Pre-early post [direct, 1 h, 24 h]: $p < .05$ Pre-late post [48 h, 72 h, 96 h]: NS	Low

Abbreviations: y, years; m, months; wk, weeks; d, days; h, hours; min, minutes; s, seconds; NS, not statistically significant; pre, baseline measurement; post, post-prism adaptation measurement; follow-up, measurement at least 3 months after last session of prism adaptation; NA, not applicable; PA, prism adaptation; SA, sham adaptation; CPA, classic prism adaptation; EPA, ecological prism adaptation; OKSP, optokinetic stimulation; %Hits, percentage of hits; %Omissions, percentage of omissions; %Perseverations, percentage of perseverations; Omdiff, omission difference score between contralesional and ipsilesional side of the search array; RT, reaction time; BIT, behavioural inattention test; RCT, randomized controlled trial.

Note. Table is sorted by quality (from high to low), and subsequently by year (from oldest to most recent).

[a]Results for all cancellation tasks together.

[b]Inconsistency in the article regarding the *p*-value. After consulting the authors, this *p*-value was adapted.

[c]One patient was excluded as her cancellation performance was close to a ceiling at baseline; hence, analyses regarding cancellation were carried out on 12 of 13 patients.

[d]Cancellation tasks were also reported. However, of those no separate scores were reported (only total scores of 6 standard cancellation tasks).

Table 8.2 Scores of the quality assessment of the discussed studies, based on 8 elements.

Study	1. Comparison of groups	2. Randomization	3. Comparable groups	4. Equal treatment	5. Blinding	6.Reporting completeness follow-up	7. Reporting time post-stroke	8. Reporting effect size	Total
Serino et al. (2009)	1	1	1	1	0	0	1	1	6
Priftis et al. (2013)	1	1	1	1	0	0	1	1	6
Rossetti et al. (1998)	1	1	1	1	0	0	1	0	5
Nys, de Haan, et al. (2008)	1	1	1	1	0	0	1	0	5
Vangkilde & Habekost (2010)	1	1	1	0	0	0	1	1	5
Mancuso et al. (2012)	1	1	1	1	0	0	1	0	5
Saevarsson et al. (2010)	1	1	0	1	0	0	1	0	4
Frassinetti et al. (2002)	1	0	1	0	0	0	1	0	3
Fortis et al. (2010)	0	0	0	0	0	1	1	1	3
Serino et al. (2007)	0	0	0	0	0	1	1	0	2
Eramudugolla et al. (2010)	0	0	0	0	0	0	1	1	2
Shiraishi et al. (2010)	0	0	0	0	0	1	1	0	2
Nijboer et al. (2011)	0	0	0	0	0	1	1	0	2
Rusconi & Carelli (2012)	0	0	0	0	0	1	1	0	2
Farnè et al. (2002)	0	0	0	0	0	0	1	0	1
McIntosh et al. (2002)	0	0	0	0	0	0	1	0	1
Morris et al. (2004)	0	0	0	0	0	0	1	0	1
Humphreys et al. (2006)	0	0	0	0	0	0	1	0	1
Rousseaux et al. (2006)	0	0	0	0	0	0	1	0	1
Vallar et al. (2006)	0	0	0	0	0	0	1	0	1
Nys, Seurinck, et al. (2008)	0	0	0	0	0	0	1	0	1
Sarri et al. (2008)	0	0	0	0	0	0	1	0	1
Keller et al. (2009)	0	0	0	0	0	0	1	0	1
Saevarsson et al. (2009)	0	0	0	0	0	0	1	0	1
Luauté et al. (2012)	0	0	0	0	0	0	1	0	1
Gossmann et al. (2013)	0	0	0	0	0	0	1	0	1
Saj et al. (2013)	0	0	0	0	0	0	1	0	1
Smit et al. (2013)	0	0	0	0	0	0	1	0	1
Keane et al. (2006)	0	0	0	0	0	0	0	0	0
Jacquin-Courtois et al. (2008)	0	0	0	0	0	0	0	0	0

0, Negative; 1, Positive. Table is sorted by quality (from high to low), and subsequently on year (from oldest to most recent). High was considered total scores ≥6, moderate 4 and 5, and low ≤3.

Elements: 1, Comparison of an experimental group and a control group; 2, Randomization of different conditions; 3, Comparable groups; 4, Equal treatment of groups (excluding intervention); 5, Blinding of effect evaluators; 6, Reporting completeness of follow-up; 7, Reporting time post-stroke; 8, Reporting effect size.

The number of PA sessions ranged from one up to daily sessions for a period of 3 months (Nijboer et al., 2011). Fourteen studies only conducted post-measurements within 24 hr after the treatment. The other 15 studies had at least one post-measurement between 24 hr and 2.5-3 years (Shiraishi et al., 2010) after the treatment. All studies with more than one session conducted sessions at least once per week with a maximum time span of 5 weeks, with the exception of the study by Humphreys et al. (2006), in which patients had two sessions per week, for 5 weeks, followed by a month break and then two sessions per week for another 4 weeks.

Patient characteristics

All studies included patients with left-sided neglect after right brain damage due to stroke. The mean time post-stroke varied from 8 days (Nys, de Haan, et al., 2008), to 11 years (Humphreys et al., 2006). In 11 studies, only patients in the chronic, and in 6 studies, only patients in the subacute phase were included.

Visual search results

Feature search tasks

Five studies used feature search tasks. In these tasks, participants have to find a target among distractors as quickly as possible and indicate its presence or location by pressing a button. Four studies used simple feature search tasks in which stimuli consisted of letters (i.e., “Q” and “O”; Morris et al., 2004), coloured circles (i.e., blue and green; Saevarsson et al., 2010, 2009), or shapes (i.e., squares and diamonds; Saj et al., 2013). The tasks of Vangkilde and Habekost (2010) were more ecologically valid, but can be seen as feature search. In the “Where is Wally” task, a character had to be found between many people. In the “cupboard” task, patients had to locate everyday objects (e.g., keys, brush) among distractors (Vangkilde & Habekost, 2010). In all feature search tasks, both accuracy and reaction time (RT) were evaluated, with the exception of the study of Morris et al. (2004), in which only RT was measured.

Accuracy: Vangkilde and Habekost (2010; moderate ranking) reported more improvement after PA than after a different type of treatment. Saevarsson et al. (2010; moderate ranking) found similar results in accuracy after a combination of PA and neck vibration therapy and vibration therapy only. Of the low-ranking studies, an improvement was found by Saj et al. (2013). Saevarsson et al. (2009) found no improvement in accuracy in the target absent condition or when both feedback and a time limit were given. Accuracy did improve in the target present condition without feedback and a time limit.

Reaction time: Vangkilde and Habekost (2010; moderate ranking) found that RTs decreased more after PA than after general cognitive rehabilitation. Saevarsson et al. (2010; moderate ranking) found comparable RTs and accuracy scores after neck vibration therapy compared to both neck vibration and PA. Within group, there was a significant improvement in RTs after the combination of neck vibration and PA therapy, while no changes were found in accuracy. No improvements were found on RT in the cancellation task. Of the low-ranking studies, no improvement in RT was found by Saj et al. (2013). Morris et al. (2004) only found an improvement for some of the patients but did not report accuracy as a measure. Saevarsson et al. (2009) found that RT decreased following PA in both experiments, with the exception of a target absent condition in one of the two experiments, while accuracy measures improved or remained the same.

Cancellation tasks

Most studies used simple pen-and-paper cancellation tasks in which letters, stars, bells, lines, balloons, or other objects had to be cancelled. These tasks were all visuo-manual: targets had to be cancelled by reaching to them. Priftis et al. (2013) used a task in which objects in a room or a picture had to be verbally reported. This task is comparable to cancellation tasks in the sense that the amounts of hits, misses, and RT were scored; however, no manual response was requested.

Omissions or hits: The number or percentage of omissions or hits was commonly used as an outcome measure. The analyses were either performed on the total search array, separately for the contralesional (and in some studies also the ipsilesional) side of the search array, or on the difference score (i.e., the difference in omissions or hits between sides).

Total number of omissions or hits: Both high-ranking studies (Priftis et al., 2013; Serino et al., 2009) found more improvement in number of hits after PA. Whereas Serino et al. (2009) found more improvement after PA than after sham adaptation, Priftis et al. (2013) compared PA treatment with visual scanning training and limb activation and found an equal improvement for all treatments.

All five moderate-ranked studies reported that patients improved more on cancellation in the PA condition than in other or no-treatment conditions on at least one task (Fortis et al., 2010; Mancuso et al., 2012; Nys, de Haan, et al., 2008; Rossetti et al., 1998; Saevarsson et al., 2010; Vangkilde & Habekost, 2010). There were 19 low-ranked studies that conducted cancellation tasks and used omissions or hits as an outcome measure. One of these did not report statistical analyses (Keane et al., 2006). Of the remaining studies, 11 found an improvement after PA (Farnè et al., 2002; Frassinetti et al., 2002; Gossmann et al., 2013; Humphreys et al., 2006; Jacquin-Courtois et al., 2008; Keller et al., 2009; McIntosh et al., 2002; Nijboer et al., 2011; Nys, de Haan, et al., 2008; Serino et al., 2007; Vallar et al., 2006). Effects were less consistent in four studies. More specifically, Sarri et al. (2008) found improvement after PA for only some of the patients. Eramudugolla et al. (2010), Shiraishi et al. (2010), and Fortis et al. (2010) found an improvement on only one of the used tasks. Luauté et al. (2012), Smit et al. (2013), and Rousseaux et al. (2006) found no improvement on cancellation.

Omissions split for side: Nys et al. (2008; low raking) and Serino et al. (2007; low ranking) evaluated the number of omissions for both sides of the search array separately. They reported an improvement for the contralesional side. Serino et al. (2007) additionally observed a significant improvement regarding omissions at the ipsilesional side, whereas in the study of Nys, Seurinck, et al. (2008) patients only had very few ipsilesional omissions, so no improvement after PA was found.

Centre of cancelation: Smit et al. (2013; low ranking) used the centre of cancellation (CoC; Rorden & Karnath, 2010), which is informative about both the number of omissions and the location of cancelled targets. No significant improvement after PA was found.

Perseverations: Nijboer et al. (2011), Nys, Seurinck, et al. (2008), and Vallar et al. (2006; all low ranking) consistently showed that the amount of perseverations was lower after PA compared to baseline.

Duration: Nijboer et al. (2011) and Smit et al. (2013) investigated the total duration for completion of the cancellation task. Besides an improvement in accuracy, Nijboer et al. (2011) found that patients with neglect became faster after PA. Smit et al. (2013) did not find an improvement in accuracy but did confirm faster search. Both studies did not use a control group to counteract learning and/or motivational effects.

General discussion and conclusion

The aim of this review was to evaluate the effect of PA on visual search in patients with neglect. Other reviews have looked into PA as a rehabilitation method for neglect in general (Fasotti & van Kessel, 2013; Newport & Schenk, 2012), PA in comparison with other rehabilitation methods (Yang et al., 2013), or to a limited extent on effects in oculo-motor exploration (Jacquin-Courtois et al., 2013), but none have specifically addressed the effect of PA on visual search. Thirty studies were included in the current review, of which 7 were rated as moderate-to-high-quality studies and 23 were rated as low-quality studies.

Visual search

Only 5 studies had the specific aim to investigate the influence of PA on visual search tasks (thus no cancellation tasks). These 5 studies all used features search tasks, in which participants have to find a target among distractors as quickly as possible. The remaining 25 studies used cancellation tasks, in which multiple targets have to be found. Perseverations can be informative about working memory deficits in visual search behaviour (Husain et al., 2001): to prevent revisits and omissions, patients have to keep track of targets that are already cancelled and simultaneously scan the remaining area. Although omissions or duration does not differentiate between sub processes of visual search, these measures are *dependent* on sub processes of visual search (e.g., search organization; Ten Brink, Van der Stigchel, et al., 2016, or spatial working memory; Husain et al., 2001). Hence, omissions and search duration might be more of a ‘compound’ measure of these sub processes. Although we recommend more specific visual search measures for future studies, like intersections between consecutive cancelled targets or search consistency (Ten Brink, Van der Stigchel, et al., 2016), we will discuss what has been found with these widely used ‘compound’ measures. The evaluation of visual search outcome measures for both feature search tasks and cancellation tasks is described below.

Feature search outcome measures

Vangkilde and Habekost (2010; moderate ranking) found improvements regarding both RT and accuracy after PA compared to general cognitive rehabilitation. Saevarsson et al. (2010) found improvements between the pre- and post-measurements in the PA combined with neck vibration group, but no additional beneficial effects compared with neck vibration only. The low-ranked studies found improvements on either both RT and accuracy (Saevarsson et al., 2009), only accuracy (Saj et al., 2013), or on RT for a subgroup of patients (Morris et al., 2004). Hence, there seems to be a beneficial effect of PA on feature search. However, as only five studies of low-to-moderate quality looked into feature search after PA, we cannot draw any strong conclusions. Monitoring the speed-accuracy trade-off would provide additional information regarding visual search efficiency.

Cancellation outcome measures

Investigating the number of omissions, all high- and moderate-ranked studies found that there was more improvement in the PA group than in the control group, with the exception of Priftis et al. (2013). Regarding omissions at the ipsilesional side, Serino et al. (2007) observed a significant decrease after PA, whereas Nys, Seurinck, et al. (2008) did not. This can be explained by a *ceiling effect,* as the patient might had already cancelled all ipsilesional targets at baseline. As some patients omitted less ipsilesional targets after PA, the ratio between the contralesional and ipsilesional side might be a less sensitive measure and is not recommended. This ceiling effect could also lessen the measured outcome when analyses are carried out on the total search array, or when the CoC measure is used.

The question remains to what extent omissions and hits are informative about visual search. As the targets do not disappear after cancellation, patients who search slowly and/or disorganized could eventually find all targets. Even though it is more likely that targets are omitted when no structured search pattern is adopted, search efficiency cannot be evaluated when only omissions are scored. Only two (low ranking) studies evaluated total duration of cancellation. Both showed that patients became faster after PA (with improved or equal accuracy). Although learning effects need to be taken into consideration, total task duration might be a useful measure in addition to number of omissions. Again, having a speed-accuracy trade-off can be informative regarding visual search efficiency. Another advantage is that no ceiling effect is expected for both duration and RT. This possibly makes these measures more sensitive, enabling them to uncover milder search impairments.

Three studies reported a decrease of perseverations after PA (Nijboer et al., 2011; Nys, Seurinck, et al., 2008; Vallar et al., 2006). This is a promising measure for the evaluation of visual search. Revisiting previously cancelled targets could indicate that their locations were not remembered, which could be related to spatial working memory or spatial remapping deficits that are commonly found in neglect (Pisella et al., 2011). However, these studies were ranked low. More studies are needed to confirm the effects.

Prism adaptation: The current state of the literature

The current state of the literature on PA mainly consists of studies that do not explicitly describe blinding of the effect evaluators and do not use specific visual search measures. A standard protocol for PA treatment is lacking. The inconsistency in (PA) procedures, the possibly biased effect evaluation, and the variety of tests for assessing neglect and/or visual search prevents us from being able to draw direct conclusions about the PA effect on visual search in neglect and to provide recommendations about the use of PA in patients with neglect. To facilitate the replication of studies and the comparison of PA protocols, we recommend providing a clear and detailed description of the PA procedure for future experimental studies. This should eventually lead to a consensus about the most beneficial protocol for PA therapy. A consensus should also be reached about a standard set of neuropsychological and experimental tests and outcome measures. Additionally, as neglect is a relatively heterogeneous disorder, a set of standard criteria regarding the inclusion of patients is needed. These criteria should also specify when to use restrictive inclusion criteria and when to aim for a broader sample.

Limitations of the current review

A limitation of the current review is that only patient studies were included. Investigating the behavioural and neuronal effects of PA-induced neglect on visual search behaviour and search efficiency in healthy participants could be informative about the mechanisms of PA on visual search. No studies were included using eye movements as an outcome measure. Eye movements could provide insight in the specific mechanisms underlying visual search deficits, such as spatial memory deficits (when locations are repeatedly fixated) or poor uptake of (contralesional) information (when targets are omitted after fixating them).

Prism adaptation and visual search organization: Suggestions for future research

The current paper reviews all outcome measures that are used to investigate the effect of PA on visual search. Although most studies did not use specific visual search tasks or measures, hence no conclusions can be drawn about the PA effect on sub processes of visual search, directions for future studies can be made.

Cancellation tasks with outcome measures such as omissions are to some extent informative about visual search but do not provide information about the subcomponents of visuospatial processing or the organization of search (e.g., visual overview, search efficiency, and search strategies). More high-quality studies looking into the effect of visual search by doing feature search or other types of visual search tasks are needed. Moreover, when cancellation tasks are conducted, we recommend to include more informative measures of search organization such as perseverations, duration of task completion, and saccadic eye movements. When measured digitally, the organization of visual search can be objectified by computing the amount of intersections with paths between previous cancelled targets, as this measure is thought to be the best to depict organization of search in a stroke population (Ten Brink, Van der Stigchel, et al., 2016).

Acknowledgements

This work was supported by the “Revalidatiefonds” under grant R2012134 to TCWN and JMAVM.

Chapter 9

Study protocol of "Prism Adaptation in Rehabilitation": A randomized controlled trial in stroke patients with neglect

Ten Brink, A. F., Visser-Meily, J. M. A., Nijboer, T. C. W. (2015). Study protocol of "Prism Adaptation in Rehabilitation": a randomized controlled trial in stroke patients with neglect. *BMC Neurology, 15,* 5.

Abstract

Background. A frequent disorder after stroke is neglect, resulting in a failure to report or respond to contralesional stimuli. Rehabilitation of neglect is important, given the negative influence on motor recovery, independence in self-care, transfers, and locomotion. Effects of prism adaptation (PA) to alleviate neglect have been reported. However, either small groups or no control group were included and few studies reported outcome measurements on the level of activities of daily living (ADL). The current ongoing RCT investigates the short- and long-term effects of PA in a large population in a realistic clinical setting. Measures range from the level of function to the level of ADL. *Methods and design.* Neglect patients in the subacute phase after stroke are randomly assigned to PA (n = 35) or sham adaptation (SA; n = 35). Adaptation is performed for 10 consecutive weekdays. Patients are tested at start of the study, 1 and 2 weeks after starting, and 1, 2, 4 and 12 weeks after ending treatment. Primary objectives are changes in performance on neuropsychological tests and neglect in ADL. Secondary objectives are changes in simulated driving, eye movements, balance, visual scanning and mobility, subjective experience of neglect in ADL and independence during ADL. *Discussion.* If effective, PA could be implemented as a treatment for neglect. *Trial registration.* This trial is registered at the Dutch Trial Register #NTR3278.

Introduction

Unilateral neglect occurs frequently after stroke, resulting in a failure to report or respond to stimulation in contralesional hemispace (25 to 30% of all stroke patients; Appelros et al., 2002; Buxbaum et al., 2004). In 40% of patients, neglect does not recover after 1 year and becomes chronic (Nijboer, Kollen, et al., 2013). Functional outcome of stroke patients suffering from neglect is worse than that of stroke patients without neglect (Nijboer, van de Port, et al., 2013; Nys et al., 2005), and motor recovery patterns are slower and more attenuated (Nijboer, Kollen, et al., 2014). As a result, many studies aim at alleviating the symptoms of neglect with different treatments such as visual scanning training, limb activation, mental imagery training, sensory stimulation, and prism adaptation (PA). The effectiveness of these treatments remains unproven and more research is needed in a realistic clinical setting (Bowen, Hazelton, Pollock, & Lincoln, 2013).

A promising treatment for neglect is PA (Barrett et al., 2012; Fasotti & van Kessel, 2013; Kerkhoff & Schenk, 2012; Luauté, Halligan, Rode, Jacquin-Courtois, & Boisson, 2006). PA was first described by Rossetti et al. (1998). Exposure to prisms produces a lateral shift of the visual field so that targets appear displaced. Adaptation to such an optical shift requires a set of successive visuo-motor pointing movements. When the prisms are removed, attention is automatically shifted to the contralesional side. Rossetti et al. (1998) demonstrated a significant reduction of spatial neglect following a brief period of PA with rightward prisms. Effects of PA have been reported across clinical tests of neglect, but also in more daily situations, such as wheelchair navigation (Jacquin-Courtois et al., 2008), mental imagery (Rode, Rossetti, & Boisson, 2001), and balance (Nijboer, Ten Brink, Van der Stoep, et al., 2014). The beneficial effects of PA have been reported to last two hours (Jacquin-Courtois et al., 2008; Làdavas et al., 2011; Rossetti et al., 1998) up to one week (Dijkerman, Webeling, ter Wal, Groet, & van Zandvoort, 2004; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002) after a single session, and even up to six weeks following repetitive PA (McIntosh et al., 2002; Nys, de Haan, et al., 2008; Shiraishi, Yamakawa, Itou, Muraki, & Asada, 2008). Additionally, long-term prism training has been reported to show long-lasting beneficial effects, from weeks (Frassinetti et al., 2002; Mizuno et al., 2011; Serino, Angeli, Frassinetti, & Làdavas, 2006; Serino et al., 2009) up to two years (Nijboer et al., 2011) after ending PA. Notwithstanding these positive results, either small groups or single cases were reported, no control group was included, and/or no measurements at the level of activities of daily living (ADL) were used.

This ongoing study is designed to answer the following primary research question: Can *early* intervention with PA ameliorate neglect both *better* and *earlier* compared to sham adaptation (SA)? Secondary questions are: (1) When are the optimal effects reached?; (2) What is the time course of beneficial effects of an intensive programme of exposure to prisms?; (3) Does PA affects neglect in simulated driving, eye movements, balance, visual scanning and mobility, subjective experience of neglect and independence during ADL?

Methods

Design

This RCT compares the effects of PA versus SA, both in addition to usual care (Figure 9.1). After the baseline measurement, patients will be randomly assigned to one of the two conditions: prism or sham. All patients will receive two weeks of daily treatment (5 days per week). Patients will be tested 7 times in total: at start of the study (T0; baseline), 1 week after starting treatment (T1), 2 weeks after starting treatment/at end of intervention (T2), 1 week after ending treatment (T3), 2 weeks after ending treatment (T4), 4 weeks after ending treatment (T5), and 12 weeks after ending treatment (T6).

This study is conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, Korea, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study is approved by the "Medisch Ethische Toetsingscommissie" of the University Medical Centre Utrecht (#12-183/O).

Patient population - inclusion and exclusion criteria

We recruit 70 patients, admitted to De Hoogstraat Rehabilitation centre (the Netherlands). Within the first two weeks of admission, a neuropsychologist administers neglect tests, and a nurse observes neglect in ADL according to the Catherine Bergego Scale (CBS) as standard stroke care. The inclusion criteria of this study are (1) clinical diagnosed symptomatic stroke (ischemic or intracerebral haemorrhagic lesion), first or recurrent; (2) neglect, indicated with neuropsychological neglect tests (shape cancellation test or line bisection test) and/or CBS; (3) 18-85 years of age; (4) sufficient comprehension and communication; (5) sufficient motivation, and (6) written informed consent. The exclusion criteria are (1) interfering psychiatric disorders and/or substance abuse; (2) expected discharge <4 weeks; and (3) physically and/or mentally unable to participate. The rehabilitation physician is consulted regarding the exclusion criteria.

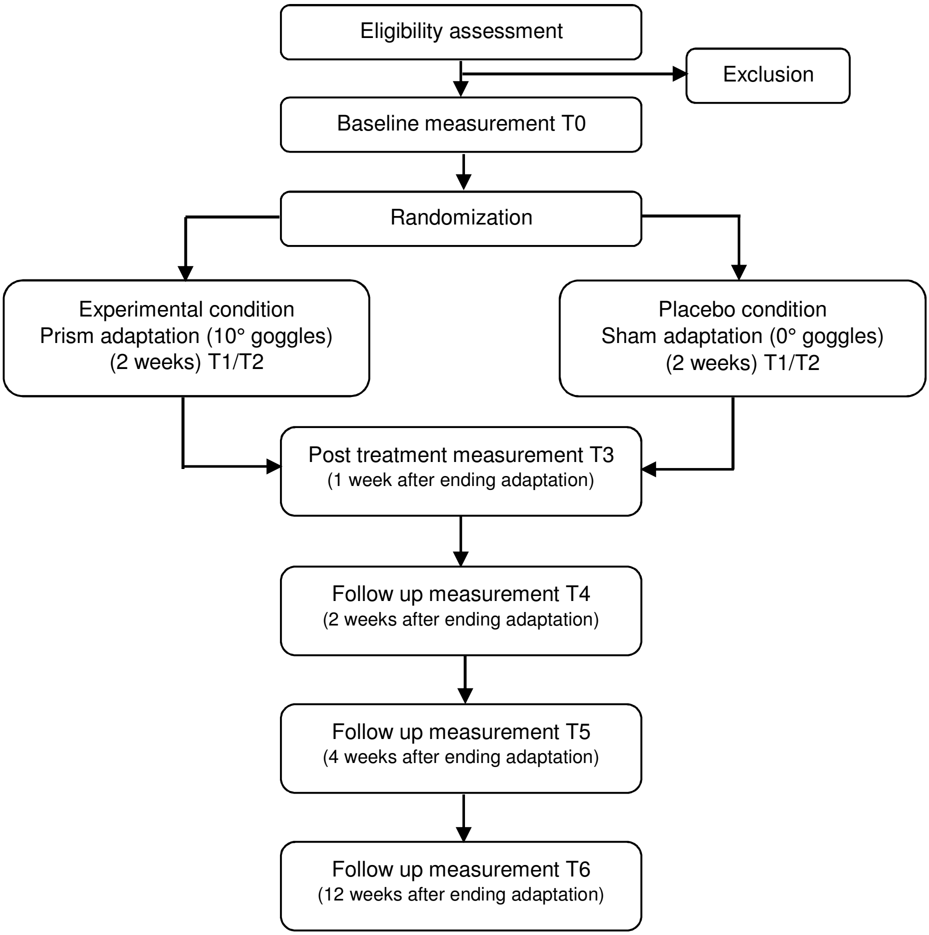

Figure 9.1 Procedure. After baseline measurement (T0), patients are randomized and receive treatment for 10 consecutive weekdays. Patients are tested after 1 week (T1), at end of treatment (T2), and 1, 2, 4 and 12 weeks after treatment (T3-T6, respectively).

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Randomization

Before start of the study, 70 printed cards with the treatment (35 PA and 35 SA) are enveloped. The investigator opens one after the baseline measurement to assign the patient to the stated treatment. Each patient will have an equal chance of being allocated to any of the conditions.

Treatment

All patients receive the current common rehabilitation programme parallel the treatment.

Experimental treatment

The PA procedure is similar to that employed by Rossetti et al. (1998), with the exception that it is repeated on 10 consecutive weekdays. Patients wear a pair of goggles fitted with wide-field point-to-point prismatic lenses, inducing a ipsilesional optical shift of 10°. Exposure consists of ±100 fast pointing movements to visual targets presented 10° to the left or right of the body midline at a distance of ±65 cm (Smit et al., 2013). A board is held under the chin to prevent viewing of the hand at its starting position, but allowing an unobstructed view of the targets and terminal errors. Next, the aftereffect is measured: patients point to the middle target with closed eyes to prevent online adjustment of the pointing movements towards the target due to visual feedback. For successful PA, a contralesional shift of ±3 cm from the target is required. The procedure is repeated when the aftereffect is less than 3 cm.

Placebo treatment

SA is performed with a pair of goggles with plain lenses (i.e., no optical shift). The procedure is the same as during PA. The 'aftereffect' is tested. No shift is expected.

Measurements

Baseline descriptors

The following admission-to-rehabilitation data are collected: demographics (age, sex, educational level), stroke characteristics (time post-stroke, hemisphere, type, stroke history [first-ever or recurrent]), motor function (Motricity Index, MI; Collin & Wade, 1990), and cognition (Mini-Mental State Examination, MMSE; Folstein et al., 1975).

Primary outcomes

Primary endpoints are changes in performance on neuropsychological neglect tests (shape cancellation, letter cancellation, line bisection, landmark test, copying, mental representation, and symmetrical photos) and neglect in ADL, as measured with the CBS (Azouvi et al., 2003; Ten Brink et al., 2013). The CBS is an observation scale for assessment of neglect in 10 everyday activities, and is administered by the physical therapist, occupational therapist and nurse.

Secondary outcomes

We administer a simple driving simulation task (van Kessel et al., 2013), and compute the average position on the road and the average deviation (swinging). Meanwhile we measure eye movements. To objectify balance, patients are asked to sit and/or stand on a Nintendo Wii™ Balance Board (Nijboer, Ten Brink, Van der Stoep, et al., 2014). Visual scanning and mobility is assessed with the Mobility Assessment Course (MAC; Verlander et al., 2000), which measures the extent to which patients visually scan targets while walking or wheelchair driving through a corridor. The course consists of targets (12 left and 12 right) and directional indicators. We measure subjective experience of neglect with the CBS self-evaluation. Finally, the nurse fills in the Barthel Index (BI; Collin et al., 1988), to measure independence during ADL.

During all sessions, neuropsychological tests, CBS, simulated driving, eye movements and balance are assessed. During even sessions, the MAC, CBS self-evaluation and BI are assessed additionally.

Data monitoring board

A data monitoring board takes part in this study.

Sample size estimates

No reliable information on the expected effect of PA on neuropsychological neglect tests or CBS scores is available. An effect size of 0.7 *SD* was used to estimate the necessary sample size. To identify a difference with a power of 80% and alpha .05 (2-sided), 35 patients per group (70 patients in total) are required for sufficient statistical power.

Blinding

The investigator who treats and tests the patients is not blind to the treatment, since she has to put on the goggles. The nurses, physical therapist, and occupational therapist filling in the CBS are unaware of the treatment. Patients cannot be blinded to the treatment, since they have to wear the goggles. However, patients are not explicitly told which treatment they receive.

Statistical analyses

Multivariate analysis: Repeated Measures Analyses are performed for each outcome measure separately, with Session (T0-T6) as within-subject variable and Treatment (PA, SA) as between-subject variable. With respect to timing of optimal effects, sessions T0-T1 and T1-T2 are compared. For longitudinal effects, joinpoint analyses are planned (Nijboer, Kollen, et al., 2013).

Discussion

Visuospatial neglect is a prevalent disorder and complicates rehabilitation. Despite PA seems a promising intervention, there is not sufficient evidence whether it ameliorates neglect, which withholds implementation. We aim to answer whether PA ameliorates neglect *better* and *earlier* compared to SA. We investigate the intervention in routine practice, to assure that the intervention works in real life settings. Other strengths of this study are the patient sample (i.e., large sample size including both young and older patients), design (i.e., intensive treatment, placebo control arm, and randomized design) and range of outcome measures (i.e., ADL measures and follow-up; Gillespie et al., 2014).

A weakness of this study is the non-blinding of the investigator. To reduce potential influence of this on the outcomes, instructions are standardized and tasks are computerized when possible. Furthermore, observations are done by therapists who are blinded for the conditions.

To conclude, in case of positive results, we could implement PA as a treatment for neglect in rehabilitation.

Acknowledgements

This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN, and the “Revalidatiefonds” under grant R2012134 to TCWN and JMAVM. The “Revalidatiefonds” approved the design of the study. NWO and the “Revalidatiefonds” have no other role regarding the data or manuscript.

Chapter 10

Prism adaptation in rehabilitation? No additional effects of prism adaptation on neglect recovery in the subacute phase post-stroke - A randomised controlled trial

Ten Brink, A. F., Visser-Meily, J. M. A., Schut, M. J., Kouwenhoven, M., Eijsackers, A. L. H., Nijboer, T. C. W. (In press). Prism adaptation in rehabilitation? No additional effects of prism adaptation on neglect recovery in the subacute phase post-stroke - A randomised controlled trial. *Neurorehabilitation and Neural Repair.*

Abstract

Background. Patients with neglect ignore or respond slower to contralesional stimuli. Neglect negatively influences independence in activities of daily life (ADL). Prism adaptation (PA) is one of the most frequently studied treatments, yet there is little evidence regarding positive effects on neglect behaviour in ADL. *Objective*. To assess whether PA in the subacute phase ameliorates neglect in situations of varying complexity. *Methods*. A total of 70 neglect patients admitted for inpatient stroke rehabilitation received either PA or sham adaptation (SA) for 2 weeks, with full access to standard treatment. There were 7 time-dependent measurements (baseline and 1-4, 6 and 14 weeks after start of treatment). The primary outcome was change of neglect as observed during basic ADL with the Catherine Bergego Scale (CBS). Secondary outcomes were changes in performance on a dynamic multitask (i.e., the Mobility Assessment Course; MAC), and a static paper-and-pencil task (i.e., a shape cancellation task; SC). *Results*. In all, 34 patients received PA and 35 SA. There were significant time-dependent improvements in performance as measured with the CBS, MAC, and SC (all $F \geq 15.57$, $p < .001$). There was no significant difference in magnitude of improvement between groups on the CBS, MAC, and SC (all $F \leq 2.54$, $p \geq .113$). *Conclusions*. No beneficial effects of PA over SA in the subacute phase post-stroke was observed, which was comparable for situations in varying complexity. Heterogeneity of the syndrome, time post-stroke onset and the content of the treatment as usual are discussed. Basic knowledge on subtypes and recovery patterns would aid the development of tailored treatment. *Trial registration*. #NTR3278.

Introduction

A frequent post-stroke disorder in lateralized attention is visuospatial neglect ("neglect"). Patients with neglect ignore – or respond slower to – contralesional stimuli, without being aware of it (Appelros et al., 2002; Buxbaum et al., 2004). Of all stroke patients, 20 to 82% shows neglect, depending on the moment and task(s) used (Chen, Chen, et al., 2015). Generally, spontaneous recovery occurs within the first 3 months post-stroke onset, but in 40% of neglect patients, the disorder is still present 1 year later (Nijboer, Kollen, et al., 2013). Neglect patients need more help in activities of daily living (ADL) compared to patients without neglect, and are less likely to be discharged home (Katz, Hartman-Maeir, Ring, & Soroker, 1999; Nijboer, van de Port, et al., 2013). Adequate treatment of neglect is, therefore, of great importance.

The current neglect treatment is mainly visual scanning training, a *compensatory* treatment with emphasis on top-down strategies (Pizzamiglio et al., 1992). Its effectivity, however, remains unproven (see for a review: Bowen et al., 2013). Additionally, several *restorative* treatments have been developed, of which prism adaptation (PA) is the most frequently studied (i.e., 16 randomised controlled trials [RCTs]; Angeli, Benassi, & Làdavas, 2004; Frassinetti et al., 2002; Làdavas et al., 2011; Mancuso et al., 2012; Mizuno et al., 2011; Nys, de Haan, et al., 2008; Priftis et al., 2013; Rode et al., 2015; Rossetti et al., 1998; Saevarsson et al., 2010; Serino et al., 2006, 2009; Spaccavento et al., 2016; Turton et al., 2010; Vaes et al., 2016; Vangkilde & Habekost, 2010). The PA paradigm was developed by Rossetti et al. (1998), and their PA procedure is used in most studies. During PA, patients wear prism glasses that produce an ipsilesional lateral shift of the visual field. Adaptation to this optical shift requires a set of successive visuo-motor pointing movements. When the prisms are removed, attention is automatically shifted contralesional. Of RCTs that included neuropsychological neglect tasks (Frassinetti et al., 2002; Làdavas et al., 2011; Mancuso et al., 2012; Mizuno et al., 2011; Nys, de Haan, et al., 2008; Priftis et al., 2013; Rode et al., 2015; Rossetti et al., 1998; Saevarsson et al., 2010; Serino et al., 2009, 2006; Spaccavento et al., 2016; Turton et al., 2010; Vaes et al., 2016; Vangkilde & Habekost, 2010), in 60%, PA diminished neglect as measured with at least one of these pen-and-paper tasks (Frassinetti et al., 2002; Làdavas et al., 2011; Nys, de Haan, et al., 2008; Rossetti et al., 1998; Saevarsson et al., 2010; Serino et al., 2006, 2009; Vaes et al., 2016; Vangkilde & Habekost, 2010). There is, however, little evidence regarding whether

PA diminishes neglect in ADL because paper-and-pencil tasks lack the dynamics and complexity of daily life (Ten Brink, Visser-Meily, et al., 2017). Of RCTs that included measures at the level of (basic) ADL (Mizuno et al., 2011; Priftis et al., 2013; Rode et al., 2015; Spaccavento et al., 2016; Turton et al., 2010; Vangkilde & Habekost, 2010), in only 33% did neglect behaviour decrease more after PA compared to no or control treatment (Mizuno et al., 2011; Vangkilde & Habekost, 2010). This inconsistency between results is probably a result of the lack of comparability between studies (e.g., treatment procedure, intensity, tasks) or a general lack of methodological quality (e.g., small groups [11-43], no right-sided neglect, measures of ADL in only 38% of studies, follow-up measurements in only 25% of studies). In sum, it is uncertain whether PA should be implemented in rehabilitation. The effectiveness of other rehabilitation interventions (e.g., limb activation training, optokinetic stimulation, eye patching) also remains unproven (Bowen et al., 2013). More high-quality (i.e., adequate statistical power, randomization, ADL measures, follow-up), pragmatic RCTs in a clinical setting are needed (Barrett et al., 2012; Bowen et al., 2013).

We conducted an RCT in which the aforementioned issues were considered. Our primary aim was to determine whether treatment with PA in the subacute phase ameliorated neglect behaviour in basic ADL (as measured with the Catherine Bergego Scale; CBS) to a larger extent compared to sham adaptation (SA). In addition, to eliminate the influence of compensation strategies, we used the Mobility Assessment Course (MAC), a dynamic multitask (Ten Brink, Visser-Meily, et al., 2017). Finally, a cancellation task was includd, which is a widely used measure for neglect (Machner et al., 2012). We included stroke patients with left- and right-sided neglect. Patients with right-sided neglect have not been included in prior trials. Finding a treatment for this group of patients is, however, necessary because consequences of left- versus right-sided neglect in ADL are largely comparable (Ten Brink, Verwer, et al., 2017).

We included patients in the subacute phase post-stroke. A general consideration for early treatment is the plasticity of the brain. Spontaneous neurobiological recovery occurs within all domains and lasts around 90 days (Nijboer, Kollen, et al., 2013; Ramsey et al., 2017). The main part of recovery during this critical period is likely driven by spontaneous recovery, and the effects of rehabilitation interventions are much smaller. They may, however, improve or extent the duration of neuroplasticity (Carey et al., 2013; Khan, Amatya, Galea, Gonzenbach, & Kesselring, 2016; Ramsey et al., 2017). A more specific consideration is that patients with neglect ignore one side of their body or space in the acute phase post-stroke, and learn not to use this side of the body or hemifield. Early treatment might minimize this learned non-use, and larger effects of PA could potentially be obtained (Nys, de Haan, et al., 2008).

Methods

Research design

A single centre, randomised, double-blind (i.e., regarding the primary outcome), parallel-group study with an allocation ratio of 1:1 (i.e., an equal number of patients was allocated to each group) was conducted (for the trial protocol, see Ten Brink et al., 2015). A rehabilitation physician was consulted by the investigator regarding the inclusion and exclusion criteria (see below). Patients gave written informed consent. The nurses, physical therapists, and occupational therapists who filled in the CBS were blind to the treatment conditions. The investigator (AFTB) who treated and tested the patients regarding the secondary outcomes was not blinded to the treatment because she had to put on the goggles. If possible, tests were computerized to increase objectivity. Patients could not be (completely) blinded to the treatment because they had to wear the goggles. However, patients were not explicitly told which treatment they received, and none of them expressed any awareness of assigned condition (after informal enquiry). Patients were tested at baseline and after 1, 2, 3, 4, 6 and 14 weeks from the start of treatment. The MAC was assessed at baseline and after 2, 4, and 14 weeks.

The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht.

Participants

Stroke patients with a clinical diagnosed symptomatic stroke (first or recurrent, ischemic or intracerebral haemorrhagic lesion) admitted consecutively to De Hoogstraat Rehabilitation centre in Utrecht, the Netherlands, were considered for inclusion. Patients had to be aged between 18 and 85 years, and have sufficient comprehension and communication skills. Patients were not included in case of interfering psychiatric disorders or substance abuse, when they were physically or mentally unable to participate, or when the expected discharge was <3 weeks.

Neglect screening

All patients were screened for neglect per usual care within the first 2 weeks after admission. Patients could enrol when they showed neglect on the shape cancellation task (SC), line bisection, *or* CBS (see subsection "Primary outcome", a CBS score of ≥6 was used as a threshold for neglect; Ten Brink et al., 2013). The SC (see subsection "Static task – SC") and line bisection were administered on a computer monitor (Van der Stoep et al., 2013). The line bisection task consisted of three horizontal lines (22° long, 0.2° thick) that were presented upper right, lower left, and in the horizontal and vertical centre. The stimulus presentation was approximately 19° wide and 5.7° high. Patients had to mark the midpoint.

The thresholds for neglect were based on the mean plus 3 *SDs* of 28 healthy individuals (Van der Stoep et al., 2013). The SC omission difference score ranged from 0 to 1.05, resulting in a threshold of ≥2. The line bisection deviations ranged from -0.77 to 0.81°, -0.85 to 0.48° and -0.89 to 0.42° for the three lines respectively. A deviation outside normal range on ≥2 lines was used as a threshold.

Apparatus

The treatment and the SC were administered using a 22-inch interactive WACOM (PL2200) tablet screen (1920 × 1080), with a screen size of 477.64 mm × 268.11 mm (Smit et al., 2013). The tablet screen was oriented horizontally and slightly tilted (18°) with an adjustable stand. Patients had to respond to stimuli by drawing on or pointing at the screen with a digital stylus. DiagnoseIS (developed by Metrisquare, the Netherlands) was used to program the SC. The tablet was controlled by a laptop (Samsung NP300E5A-S01NL).

Intervention

The PA procedure was adapted from Rossetti et al. (1998). Patients wore a pair of goggles fitted with wide-field point-to-point prismatic lenses, inducing an ipsilesional optical shift of 10° (PA) or goggles with plain lenses (SA). Exposure consisted of ±100 fast pointing movements to three stimuli (red, yellow, blue) presented on a horizontal axis at a distance of ±65 cm (Smit et al., 2013). The left and right stimuli were located 10° away from the body midline. The investigator indicated which stimulus was the target. A board was held under the chin to prevent viewing of the hand at its starting position but allowing an unobstructed view of the targets and terminal errors. The coordinates of the touch responses were recorded.

Immediately after ending the adaptation phase (either PA or SA), the aftereffect of adaptation was measured. The goggles were removed, and patients were instructed to look at the central visual target. After a few seconds, patients had to point to the central target with closed eyes to prevent online adjustment of the pointing movement due to visual feedback. For successful PA, a contralesional shift of ±3 cm from the target was required. For patients in the PA group, the procedure was repeated once with ±50 pointing movements when the aftereffect was <3 cm.[4]

The treatment was performed in the rehabilitation centre once a day, each working day, for 2 weeks in addition to usual care. Usual care differed per patient, and contained ±4-6 therapy's (e.g., physical, occupational, speech; 30-60 min) per working day. Neglect treatment consisted of psycho-education and visual scanning training (i.e., search tasks and reading), 1 hour per week, 1 to 6 weeks (3 on average). In addition, during the other therapies and during ADL, patients were occasionally stimulated to attend their neglected side.

Randomisation

Before the start of the study, the investigator put 70 printed cards with the treatment condition (35 PA and 35 SA) in envelopes. After completion of the baseline assessment, the investigator opened an envelope and allocated the patient based on the treatment written on the card.

Primary outcome

The CBS is an observation scale for neglect behaviour in ADL (Azouvi et al., 1996; Ten Brink et al., 2013). Neglect severity was scored for each of 10 items on a scale of 0 (no

[4] In the PA group, 12 patients obtained an aftereffect of less than 3 cm in >50% of sessions (despite the 50 additional pointing movements). In the SA group, 1 patient pointed more than 3 cm next to the target in >50% of sessions.

neglect) to 3 (severe neglect) by a nurse, physical therapist, and occupational therapist. Items that were impossible to score (e.g., because patients were unable to independently perform the activity or the situation was not observed) were considered invalid and were not included in the total score. For the first four items, the score provided by the nurse was used; for the last six items, the average score of the three disciplines was used. The total score was the sum of the (weighted) item scores, divided by the number of valid items, multiplied by 10 (resulting in a total score ranging from 0 to 30) (Azouvi et al., 1996; Ten Brink et al., 2013). In case five or fewer items were observed, the total score was considered not reliable and therefore a missing value.

Secondary outcomes

Dynamic task – Mobility Assessment Course

Patients were instructed to walk or navigate their wheelchair independently at a leisurely pace through a corridor, without stopping or turning back (see Ten Brink et al., 2017 for a detailed description). Meanwhile, patients had to point out targets (12 per side, yellow, 10 x 10 cm). It was emphasized that there was no time limit, and finding all targets was the main goal. Task assessment lasted approximately 5 minutes. The asymmetry score was computed as the absolute difference between the number of omissions, left versus right.

Static task – Shape Cancellation

The SC consisted of 54 small targets, 52 large distractors, and 23 words and letters (Smit et al., 2013). Patients were instructed to cancel all targets. No time limit was given. The absolute difference in the number of omissions between the left and right sides of the stimulus field (asymmetry score) was computed.

Patient characteristics

We reviewed the patient's medical record and captured demographic (age, sex) and stroke-related characteristics (date stroke, stroke history, stroke type, lesion side). Global cognitive functioning was screened with either the Mini-Mental State Examination (MMSE; Folstein et al., 1975) or the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). We converted MMSE scores into MoCA scores to create a single, pooled MoCA score ([1.124 * MMSE] – 8.165) (Solomon et al., 2014). Quality of communication was determined with the "Stichting Afasie Nederland" test (SAN; Deelman et al., 1981), an observation scale for language communication. Muscle strength was measured by the Motricity Index, a short task to assess the loss of strength in the arm and leg (Collin & Wade, 1990). Independence in ADL was assessed using the Barthel Index (Collin et al., 1988). Independence in walking was evaluated with the Functional Ambulation Categories (FAC; Holden, Gill, Magliozzi, Nathan, & Piehl-Baker, 1984).

Data analyses

Power

An effect size of 0.70 *SDs* was used to estimate the necessary sample size. To identify a difference with a power of 80% and alpha .05 (2-sided), 35 patients per group (70 patients in total) were required for sufficient statistical power (Ten Brink et al., 2015).

Demographic and stroke related characteristics

Non-parametric Mann-Whitney and Chi-square tests were used to compare demographic and stroke-related characteristics between groups. Baseline neglect variables were compared with a *t*-test when data were normally distributed, and with a Mann-Whitney test when data were not normally distributed.

Outcome analyses

The analyses were conducted by the available-case, intention-to-treat method; that is, all data were included in the analysis, and the data were analysed with all patients remaining in the treatment group to which they were initially randomised. A linear mixed-effects model analysis was performed in IBM SPSS Statistics version 23 (IBM Corp., 2015) for each outcome measure separately. We choose this approach as it is appropriate for repeated measures in a heterogeneous group, the variable time is treated as a continuous measure (which is an advantage since intervals differed between measurements), patients with missing data are included, and covariates can be introduced (Goedert, Boston, & Barrett, 2013). The linear mixed-effects model used a heterogeneous first-order autoregressive covariance structure and included a random intercept for each patient. Missing data were handled by a maximum likelihood algorithm under the assumption that the missingness was random. The predictors of theoretical interest were the effects of time and group and the interaction between time and group. These predictors were included in the basic model. The quadratic relation of time, baseline score, number of days post-stroke, sex, and age were introduced as potential covariates (fixed effects). This was regardless whether or not these variables differed between groups, to enhance the fit of the model. To statistically compare the fit of each new model with the old model, the change in -2 log-likelihood (χ^2_{Change} = -$2LL_{old}$ – -$2LL_{new}$) was assessed in light of the number of additional parameters (df_{Change} = k_{Old} – k_{New}) (Field, 2013). The coefficients of the best-performing model were reported (thus, the included covariates could differ between final models, depending on their significance). Significance was set to p = .05.

Secondary analyses were performed in subgroups of patients with right-sided brain damage and moderate to severe neglect on the given task (resulting in different subgroups per task) to compare current results to prior studies and to correct for possible ceiling effects in the outcome measures. Moderate to severe neglect was defined as a CBS baseline score of ≥7 (Turton et al., 2010), MAC asymmetry score of ≥3 (Ten Brink, Visser-Meily, et al., 2017), and SC asymmetry score of ≥4 (Vaes et al., 2016). Finally, analyses were repeated with the size of the absolute aftereffect (average of all sessions) as factor, instead of group.

Results

Patient characteristics

Recruitment to the trial was carried out from November 2013 to November 2016; the final follow-up measurement took place March 2017. A total of 581 stroke patients were admitted to the rehabilitation wards during the period of recruitment (Figure 10.1). A total of 70 patients were included in the study, among one patient who quit during the baseline measurement and was neither randomised nor treated. Two patients in the PA group did not complete the treatment due to illness or early discharge (both after five sessions).

The groups were comparable with respect to patient characteristics (Table 10.1; see Supplementary Table 10.1 for characteristics of patients with right brain damage). Because patients could be included based on abnormal performance on one of neglect tasks (Supplementary Table 10.2), not all patients showed neglect on all outcome measures when they entered the trial. SC scores at baseline were not normally distributed, so a non-parametric test was used. Overall, scores on neglect measures at baseline were comparable between groups. Raw mean scores for separate patient groups (i.e., overall group, right-sided lesions, and left-sided lesions) are depicted in Table 10.2. Within the right-sided lesions group, patients in the SA group obtained higher baseline CBS scores compared to patients in the SA group.

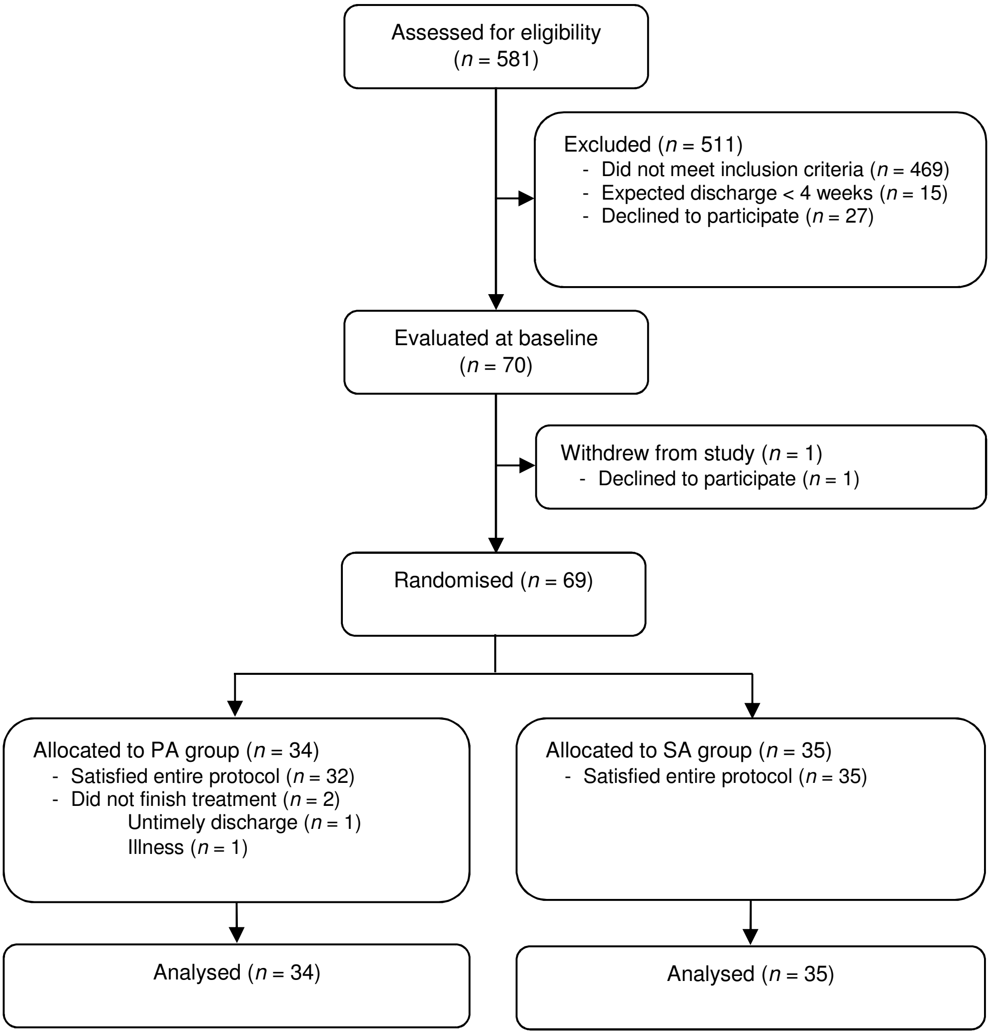

Figure 10.1 **Participant flow through the study.**

Table 10.1 Median (IQR) demographic and stroke-related characteristics at admission, and mean (SD) neglect variables at baseline, split per group.[1]

Outcome	*n*	PA	*n*	SA	Comparison
		Median (IQR)		*Median (IQR)*	
Age, years	34	59.31 (14.45)	35	61.48 (13.37)	$U = 594$, $z = -0.01$, $p = .990$
Sex, % male	34	74	35	69	$X^2(1, N = 69) = 0.21$, $p = .650$
Time post-stroke onset (at baseline), days	34	41.50 (39.00)	35	37.00 (37.00)	$U = 566$, $z = -0.35$, $p = .728$
Length of stay, days	34	89.50 (55.00)	35	99.00 (50.00)	$U = 497.5$, $z = -1.17$, $p = .242$
Stroke history, % first	32	84	29	90	$(1, N = 61) = 0.37$, $p = .542$
Stroke type, %	28		29		$X^2(1, N = 57) = 1.23$, $p = .541$
- Ischemic		68		76	
- Intracerebral haemorrhage		29		17	
- Subarachnoid haemorrhage		4		7	
Lesion side, %	34		33		$X^2(1, N = 67) = 0.40$, $p = .819$
- Left		21		21	
- Right		77		73	
- Bilateral		3		6	
Neglect side, % left	34	82	35	77	$X^2(1, N = 69) = 0.29$, $p = .591$
MoCA (0-30)	27	19.94 (6.80)	29	18.81 (5.60)	$U = 383$, $z = -0.14$, $p = .889$
SAN (1-7)	28	6.00 (2.00)	32	6.00 (2.40)	$U = 389.5$, $z = -0.91$, $p = .366$
Barthel Index (0-20)	28	7.75 (6.00)	32	7.00 (7.00)	$U = 409$, $z = -0.58$, $p = .562$
Motricity Index arm (0-100)	25	39.00 (76.00)	28	0 (75.00)	$U = 312.5$, $z = -0.71$, $p = .476$
Motricity Index leg (0-100)	26	72.00 (83.00)	29	52.00 (75.00)	$U = 345.5$, $z = -0.54$, $p = .588$
Functional Ambulation Categories (0-5)	33	2.50 (2.00)	35	3.00 (1.50)	$U = 536.5$, $z = -0.51$, $p = .609$

Neglect variables at baseline					
SC, absolute asymmetry	34	2 (7)	35	1 (12)	U = 577.5, z = -0.21, p = .831
		Mean (SD)		*Mean (SD)*	
CBS	34	12.83 (6.62)	34	15.43 (7.54)	$t(66)$ = -1.51, p = .136
MAC, absolute asymmetry	33	3.91 (3.52)	33	5.30 (3.49)	$t(64)$ = -1.61, p = .112

Abbreviations: CBS, Catherine Bergego Scale; IQR, interquartile range; MAC, Mobility Assessment Course; MoCA, Montreal Cognitive Assessment; PA, prism adaptation; SA, sham adaptation; SAN, Stichting Afasie Nederland; SC, shape cancellation task.

[1]Group sizes differ among measures due to missing data.

Table 10.2 Mean (*SD*) neglect scores per week, split for experimental group (PA and SA) and lesion side (total group, right and left-sided lesions).[1]

		Week 0		Week 1		Week 2		Week 3		Week 4		Week 6		Week 14	
		n	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)
CBS															
Tot.	PA	34	12.83 (6.62)	30	12.19 (6.03)	29	11.74 (6.46)	28	10.22 (6.00)	29	9.02 (5.54)	28	9.46 (5.46)	-	-
	SA	34	15.43 (7.54)	35	12.31 (8.26)	34	11.97 (8.34)	33	11.68 (7.88)	32	10.88 (7.25)	30	11.04 (7.94)	-	-
R	PA	26	13.76 (6.70)	22	13.38 (5.81)	21	12.92 (6.02)	20	11.84 (5.38)	21	10.41 (4.84)	21	10.53 (4.93)	-	-
	SA	23	18.08 (7.23)	24	15.03 (8.06)	23	14.01 (8.45)	24	13.46 (7.91)	22	12.91 (7.42)	21	13.53 (8.06)	-	-
L	PA	7	8.45 (4.55)	7	7.61 (4.74)	7	6.39 (3.20)	7	4.31 (2.82)	7	3.64 (3.48)	6	4.21 (3.01)	-	-
	SA	7	10.86 (5.02)	7	8.07 (5.08)	7	7.60 (5.94)	6	6.87 (6.00)	7	6.36 (4.14)	7	4.87 (2.33)	-	-
MAC															
Tot.	PA	33	3.91 (3.52)	-	-	29	3.94 (3.26)	-	-	27	3.27 (3.07)	-	-	21	2.51 (2.28)
	SA	33	5.30 (3.49)	-	-	34	4.12 (3.61)	-	-	30	4.53 (3.46)	-	-	28	3.03 (2.67)
R	PA	25	4.48 (3.64)	-	-	22	4.74 (3.27)	-	-	21	3.91 (3.18)	-	-	17	2.99 (2.27)
	SA	24	6.12 (3.18)	-	-	24	5.13 (3.38)	-	-	22	5.41 (3.39)	-	-	19	3.73 (2.47)
L	PA	7	1.29 (0.95)	-	-	7	1.43 (1.51)	-	-	6	1.03 (0.94)	-	-	4	0.50 (0.58)
	SA	5	3.69 (4.52)	-	-	6	1.99 (3.95)	-	-	6	2.17 (2.86)	-	-	6	1.33 (2.80)
SC															
Tot.	PA	34	4.56 (5.72)	34	3.41 (5.05)	31	4.03 (6.66)	29	3.10 (4.91)	28	2.50 (3.93)	29	3.03 (4.79)	22	1.14 (1.98)
	SA	35	6.31 (8.41)	35	5.80 (7.72)	35	4.63 (6.40)	34	4.53 (7.02)	32	4.06 (7.09)	33	2.85 (5.87)	32	2.16 (4.54)
R	PA	26	5.08 (5.48)	26	3.62 (4.74)	24	5.17 (7.20)	22	4.00 (5.35)	22	3.05 (4.27)	23	3.74 (5.16)	18	1.28 (2.16)
	SA	24	8.75 (9.11)	24	8.00 (8.45)	24	6.33 (7.02)	24	6.08 (7.84)	23	5.13 (7.86)	23	3.87 (6.81)	22	3.00 (5.29)
L	PA	7	0.57 (0.79)	7	0.57 (1.13)	7	0.14 (0.39)	7	0.29 (0.49)	6	0.50 (0.84)	6	0.33 (0.52)	4	0.50 (0.58)
	SA	7	1.43 (2.51)	7	1.14 (1.35)	7	0.86 (2.27)	7	1.00 (1.41)	7	1.57 (4.16)	7	0.57 (0.79)	7	0.43 (0.54)

Abbreviations: CBS, Catherine Bergego Scale; L, left-sided lesions; MAC, Mobility Assessment Course; PA, prism adaptation; R, right-sided lesions; SA, sham adaptation; SC, shape cancellation task; Tot., total group.

[1]Group sizes differ among measures due to missing data.

Primary outcome: Influence of prism adaptation on basic ADL

CBS scores could not be obtained after 14 weeks because most patients were discharged home. The final model included baseline score, days post-stroke and sex as confounders (Table 10.3). Overall, CBS scores improved over time, $F(1, 239) = 38.90$, $p < .001$. There was no main effect of experimental condition, $F(1, 148) = 2.54$, $p = .113$, indicating that the effects of PA and SA on the CBS scores were comparable. Additionally, no interaction effect, $F(1, 239) = 2.28$, $p = .133$ was observed, indicating that the pattern of improvement through time was comparable for PA and SA (Figure 10.2).

Sub-analyses for patients with right-sided brain damage and moderate to severe neglect ($n = 21$ in the PA group, $n = 21$ in the SA group), and with aftereffect as factor, resulted in similar findings (Supplementary Tables 10.3 and 10.4).

Table 10.3 **Fixed-effect predictors and covariates for predicting the CBS total score across weeks 1 to 6 (*n* = 69).**

Predictor	β	SE_{β}	95% CI	*p*
Group (PA)[1]	1.81	1.14	-0.44 to 4.05	.113
Time	-0.53	-0.16	-0.83 to -0.22	.001
Time * Group	-0.34	0.22	-0.78 to 0.10	.133
Baseline CBS	0.74	0.06	0.61 to 0.86	< .001
Days post-stroke	0.04	0.02	0.00 to 0.07	.024
Sex (male)	-1.98	0.98	-3.92 to -0.02	.047

Abbreviations: CBS, Catherine Bergego Scale; PA, prism adaptation.

[1]The Beta coefficient for the predictor 'Group' indicates that the predicted CBS score is on average 1.81 points higher for the PA group compared to the SA group, although this effect is not significant.

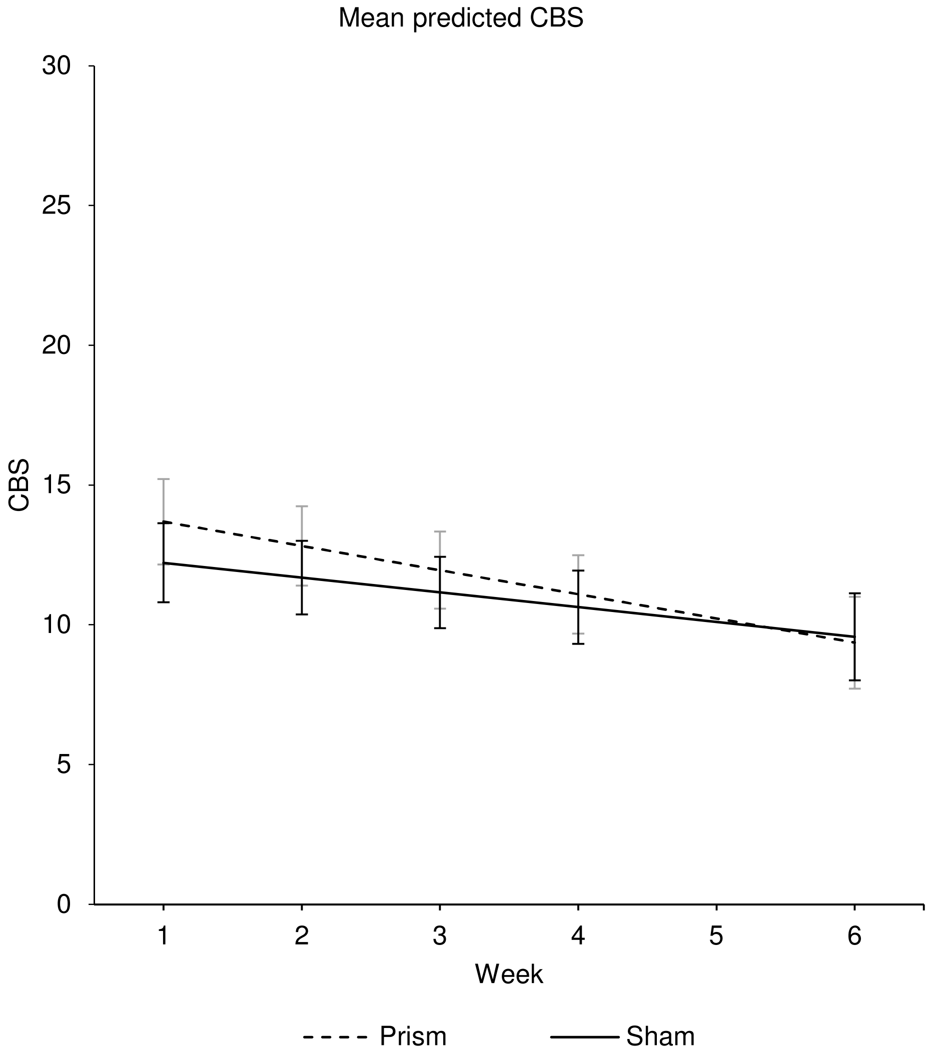

Figure 10.2 The average model predicted CBS scores and confidence intervals across assessment sessions for each group: PA (dashed line) and SA (solid line). The assessment session in week 1 occurred after 1 week of treatment and the assessment session in week 2 occurred after 2 weeks of treatment. Lower scores indicate less severe neglect. Note that scores were corrected for the confounders in the model, including the baseline CBS score. The linear mixed-effects model analysis takes into account the underlying model of the data, correcting for covariates (e.g., baseline score and days post-stroke) and missing data, therefore, reporting these data points are preferred over observed means.
Abbreviations: CBS, Catherine Bergego Scale, PA, prism adaptation; SA, sham adaptation.

Secondary outcomes: Influence of prism adaptation on lateralized attention

The final model for the **MAC** included the confounder baseline score (Table 10.4). Overall, patients improved over time with regard to MAC scores, $F(1, 110) = 17.53$, $p < .001$. No effect of experimental condition was found, $F(1, 129) = 0.70$, $p = .406$, indicating that the effects of PA and SA on the MAC scores were comparable. In addition, no interaction effect was seen, $F(1, 110) = 0.04$, $p = .851$, indicating that the pattern of improvement on MAC scores through time was comparable between groups. Comparable results were obtained when analyses were performed for patients with right-sided brain damage and moderate to severe neglect ($n = 15$ in the PA group, $n = 20$ in the SA group), and with aftereffect as factor (Supplementary Tables 10.5 and 10.6).

The final model for the **SC** included the confounder baseline score (Table 10.5). Overall, scores on the SC improved over time, $F(1, 311) = 15.57$, $p < .001$. There was no effect of group, $F(1, 105) = 0.19$, $p = .661$, indicating that SC scores did not differ between patients who received PA compared to SA. Furthermore, no interaction effect was seen, $F(1, 311) = 3.65$, $p = .057$, indicating that PA and SA had no differential effects on the pattern of improvement. Similar results were found when analyses were performed for patients with right-sided brain damage and moderate to severe neglect ($n = 12$ in the PA group, $n = 14$ in the SA group), and with aftereffect as factor (Supplementary Table 10.7 and 10.8).

Table 10.4 **Fixed-effect predictors and covariates for predicting the MAC asymmetry score across assessment in weeks 2, 4 and 14 (*n* = 69).**

Predictor	β	$SE_β$	95% CI	*p*
Group (PA) [1]	0.45	0.54	-0.62 to 1.53	.406
Time	-0.11	0.04	-0.18 to -0.04	.003
Time * Group	-0.01	0.06	-0.12 to 0.10	.851
Baseline MAC	0.65	0.06	0.53 to 0.77	< .001

Abbreviations: MAC, Mobility Assessment Course; PA, prism adaptation.

[1]The Beta coefficient for the predictor ‘Group’ indicates that the predicted MAC asymmetry score is on average 0.45 points higher for the PA group compared to the SA group, although this effect is not significant.

Table 10.5 Fixed-effect predictors and covariates for predicting the SC asymmetry score across weeks 1 to 14 (*n* = 69).

Predictor	β	SE_β	95% CI	*p*
Group (PA) [1]	-0.42	0.95	-2.29 to 1.46	.661
Time	-0.27	0.06	-0.38 to -0.15	< .001
Time * Group	0.17	0.09	-0.01 to 0.35	.057
Baseline SC	0.50	0.06	0.38 to 0.62	< .001

Abbreviations: PA, prism adaptation; SC, shape cancellation task.

[1]The Beta coefficient for the predictor 'Group' indicates that the predicted SC asymmetry score is on average 0.42 points lower for the PA group compared to the SA group, although this effect is not significant.

Discussion

In the current study, 69 stroke patients received ten sessions of either PA or SA during their admission for inpatient rehabilitation. We measured neglect behaviour in situations of varying complexity. Overall, a time-dependent improvement of neglect behaviour was observed on all measures (i.e., CBS, MAC, and SC), but no differences were found between PA and SA groups. Comparable results were found when we subsequently performed sub analyses including only patients with moderate to severe neglect and right hemisphere lesions, or with aftereffect as a factor.

How do these results relate to earlier findings? We evaluated five RCTs (of which two are recent; Rode et al., 2015; Vaes et al., 2016), that were comparable to ours regarding the time post-stroke onset (1-2 months on average), intensity of the treatment (4 to 20 sessions) and inclusion of a control group (SA; Mizuno et al., 2011; Nys, de Haan, et al., 2008; Rode et al., 2015; Turton et al., 2010; Vaes et al., 2016). Only two of these used the CBS to measure neglect behaviour in ADL. In these studies, no beneficial effects of PA over SA were reported (Mizuno et al., 2011; Turton et al., 2010). These results should, however, be interpreted with caution, as it was estimated by Turton et al. (2010) that inclusion of at least 32 patients in total is necessary to observe clinically relevant treatment effects on the CBS, which was not the case in these studies. In our study – with a larger sample of patients (*n* = 69) – , however, no treatment effects were found either. Two prior studies used the Functional Independence Measure (FIM). Here, long-term positive effects of PA were seen in one study (for mild neglect only; Mizuno et al., 2011), but not in another (Rode et al., 2015). Although all early studies (including ours) reported improvement in basic ADL over time, it is uncertain to what extent this change is related to an actual improvement of the core deficit in neglect: lateralized inattention. Because only basic activities are observed with the CBS and FIM, improvement could relate to the use of compensatory strategies, especially since many of these basic activities are practiced daily during inpatient rehabilitation. In all five studies, the lateralized attention deficit was also measured with (different) neuropsychological neglect tasks. In general (with the exception of positive findings on a few tasks), no beneficial effects of PA were found directly after treatment (Mizuno et al., 2011; Turton et al., 2010) or during follow-up compared to SA (Mizuno et al., 2011; Nys, de Haan, et al., 2008; Rode et al., 2015; Turton et al., 2010; Vaes et al., 2016). With cancellation tasks, in which no time limit is provided, compensation strategies are quite easily incorporated. Results on dynamic multitasks in a daily life environment, such as the MAC in our RCT, have not been reported yet. Visual search while moving (MAC) is not used in daily routines, such as basic ADL, and it is more dynamic in nature compared to neuropsychological tests (Ten Brink, Visser-Meily, et al., 2017). Nevertheless, no difference was seen between groups on MAC performance in the current study. Because it is a fairly new test, it remains to be seen to what extent this task is insensitive to compensation strategies or leaves less room for compensation. In sum, in most *early onset* RCTs, few beneficial effects of PA over SA are reported. This is in sharp contrast with the RCTs in the later and/or chronic phase, in which positive effects of PA compared to SA (or no treatment) were reported on at least one outcome measure in all studies (Angeli et al., 2004; Frassinetti et al., 2002; Làdavas et al., 2011; Rossetti et al., 1998; Serino et al., 2009; Vangkilde & Habekost, 2010), but one (Mancuso et al., 2012). Note that this is a rough comparison because studies differed regarding treatment characteristics, such as intensity. However, looking at studies with low (1 session in total; Angeli et al., 2004; Rossetti et al., 1998; Saevarsson et al., 2011) versus high (5 sessions per week; Mancuso et al., 2012; Turton et al., 2010) intensity does not suggest that a higher intensity results in better outcome.

It has been argued that SA (the control treatment) is a form of visuo-motor training and could, therefore, also diminish neglect (Làdavas et al., 2011). The SA procedure requires the patient to plan and perform a series of movements toward stimuli in the ipsilesional and contralesional fields. Half of the movements (i.e., towards contralesional stimuli) might train the orientation of the sensorimotor system towards the neglected side. The study of Serino et al. (2009), however, indicated that patients wearing sham goggles improved only a little, whereas their performance on neuropsychological tests greatly improved when they subsequently received PA. In several other studies, no improvement was found in the SA group, whereas the PA group improved (Angeli et al., 2004; Rossetti et al., 1998; Vangkilde & Habekost, 2010). It seems, therefore, more likely that other factors lead to recovery of patients receiving SA.

Timing of treatment, therefore, seems to be the crucial factor for significant beneficial effects of PA. In the first 3 months post-stroke, a neglect patient group is more heterogeneous compared with a later stage. There are two important mechanisms that may enhance the heterogeneity: first, spontaneous neurobiological recovery in the first 3 months post-stroke onset is variable between patients (Nijboer, Kollen, et al., 2013; Winters, van Wegen, Daffertshofer, & Kwakkel, 2017). About half of patients with neglect in the first week post-stroke, do not show neglect as measured with a cancellation task 12 weeks later (Nijboer, Kollen, et al., 2013). Second, treatment responsiveness on the existing multidisciplinary rehabilitation program could differ between patients. In particular, the visual scanning training may have the largest impact on the use of compensation strategies to avoid impairment during (simple) activities in daily living due to the lateralized attention deficit (see above). In the chronic phase, therefore, the group is more homogeneous compared with the early phase because the quick-recovering patients are not included.

Evaluating intervention effects (of PA or other interventions) for neglect on a group level in such a heterogeneous group might not be the most appropriate approach. Future studies should focus on tracing factors that determine individual differences between patients (e.g., data-driven [cluster] analyses), and, hence, patterns of recovery at the subgroup level (e.g., van Mierlo et al., 2017). Subsequently, the choice of treatment could be based on this knowledge (several examples exists in literature on drug treatment, e.g., Leyens, Reumann, Malats, & Brand, 2017). Such studies are needed in rehabilitation research too because data-driven analyses allow the generation of new hypotheses. This is necessary because the current approach has not resulted in evidence - or only to a limited extent - on beneficial effects of neglect treatment in the subacute phase post-stroke onset.

Alternatively, a theory-driven approach could be used to diminish heterogeneity of the syndrome when the focus of the study is aimed at specific subtypes of neglect, such as region-specific neglect (Aimola et al., 2012; Van der Stoep et al., 2013), or distinctions between perceptual awareness versus neglect in action planning and execution (Barrett et al., 2012; Goedert, Chen, Boston, Foundas, & Barrett, 2014). In addition, patients who are likely to benefit from PA could be differentiated based on brain properties. Lesion data or data regarding brain networks could be used into both a theory-driven approach, as different neglect subtypes likely have a different neuroanatomical basis, as well as a data-driven approach, based on patterns of recovery in patients with different lesion locations (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Gossmann et al., 2013; Redding, Rossetti, & Wallace, 2005; Serino et al., 2006). For example, lesions in the cerebellum (Redding et al., 2005), or (wide) lesions in the occipital lobe (Serino et al., 2006) seem to limit the effect of PA. Notwithstanding the theoretical importance of such distinctions, analysing smaller subgroups was currently not feasible statistically. Future trials should include measures that allow differentiation between such subtypes and/or lesion sites to reveal which patients benefit from the studied treatment.

Finally, since neglect is a multifaceted disorder, the best treatment might involve combinations of different therapeutic techniques (Fasotti & van Kessel, 2013; Kerkhoff & Schenk, 2012). A review study regarding this topic concluded that combined treatments led to larger beneficial effects compared to individual treatments (the phase of treatment was not specified; Saevarsson et al., 2011). However, more basic knowledge on the best timing of neglect treatment and individual recovery patterns is needed first to aid the development of evidence-based tailored treatment.

Strengths and limitations

A large number of neglect patients was included and almost no patients dropped out during treatment or were lost to follow-up. This can be considered a strength, as the treatment should eventually be integrated within the current rehabilitation program. This was the first study in which patients with right-sided neglect after left hemisphere lesions were included. The strength of the study (i.e., all neglect patients in the subacute phase were included) is, however, at the same time a limitation, as the heterogeneity of the group could have prevented us from finding (subtle) effects of PA. Patients were tested only for neglect, thus, visual field defects were not detected. Positive effects of PA on neglect in patients with comorbid hemianopia, however, have been reported (Nys, de Haan, et al., 2008). In addition, as patients were randomized, we did not expect comorbid visual field defects to affect our results.

An important drawback of a study that is performed as part of an existing rehabilitation programme is the lack of control regarding other treatments. In the current rehabilitation centre, neglect treatment consisted of 1 hr of visual scanning training per week, in combination with efforts made by the complete team during every day, throughout the admission (e.g., physical and occupational therapists, as well as nursing staff trying to enhance attention for the neglected side). The intensity of the usual care might therefore differ between individual patients, depending on the severity of neglect and treatment sessions (physical, occupational, etc.) per day. At group level, however, estimations are that the groups received largely comparable amounts of neglect training and feedback on a daily basis.

A final limitation is the difference between SA and PA groups at baseline, for patients with right-sided lesions. Patients in the SA group obtained higher CBS scores (indicating more severe neglect) compared to patients in the PA group. SA patients had, therefore, more 'potential of rehabilitation', which could, possibly, have affected our results. In order to minimize this effect, we have corrected for baseline score in our models.

Conclusions

No time-dependent beneficial effects were found in a large sample of neglect patients after PA compared to SA, in the subacute phase post-stroke. Possibly, PA is no effective treatment for neglect in the subacute phase. It could, however, also relate to the heterogeneity of the neglect syndrome, enhanced by neurobiological recovery or standard treatment effects. To conclude, we found no evidence that PA should replace the current treatment for neglect in the subacute phase post-stroke.

Acknowledgements

This work was supported by the NWO (Netherlands organization for Scientific Research) under grant 451-10-013 to TCWN, and the "Revalidatiefonds" under grant R2012134 to TCWN and JMAVM. The "Revalidatiefonds" approved the design of the study. NWO and the "Revalidatiefonds" have no other role regarding the data or manuscript. We would like to thank all patients who participated in this study and the nurses, occupational therapists and physical therapists who observed the patients throughout the study.

Supplementary Table 10.1 Median (IQR) demographic and stroke related characteristics at admission, for right brain damaged patients only, split per group.[1]

Outcome	*n*	PA	*n*	SA	Comparison
Age, years	26	61.46 (12.49)	24	62.09 (13.04)	$U = 304$, $z = -0.16$, $p = .877$
Sex, % man	26	73.1	24	62.5	$X^2(1, N = 50) = 0.64$, $p = .423$
Time post-stroke onset (at baseline), days	26	41.50 (45.00)	24	43.50 (39)	$U = 308$, $z = -0.08$, $p = .938$
Length of stay, days	26	85.50 (70.00)	24	108.50 (49.00)	$U = 231.5$, $z = -1.56$, $p = .188$
Stroke history, % first	24	87.5	20	85.0	$X^2(1, N = 44) = 0.06$, $p = .810$
Stroke type, %	23		19		$X^2(1, N = 42) = 0.66$, $p = .720$
- Ischemic		69.6		78.9	
- Intracerebral haemorrhage		26.1		15.8	
- Subarachnoid haemorrhage		4.3		5.3	
Neglect side, % left	26	100	24	100	-
MoCA (0-30)	21	21.00 (6.40)	22	18.81 (6.00)	$U = 193.5$, $z = -0.91$, $p = .361$
SAN (1-7)	22	6.00 (1.30)	21	6.00 (2.00)	$U = 214$, $z = -0.44$, $p = .662$
Barthel Index (0-20)	21	8.00 (7.00)	22	6.25 (7.00)	$U = 173$, $z = -1.41$, $p = .158$
Motricity Index arm (0-100)	18	66.50 (80.80)	18	7.00 (56.50)	$U = 119$, $z = -1.41$, $p = .157$
Motricity Index leg (0-100)	19	75.00 (74.00)	18	52.00 (75.00)	$U = 142$, $z = -0.90$, $p = .368$
Functional Ambulation Categories (0-5)	25	3.00 (2.30)	24	2.75 (2.00)	$U = 253.5$, $z = -0.94$, $p = .346$

Abbreviations: IQR, interquartile range; MoCA, Montreal Cognitive Assessment; PA, prism adaptation; SA, sham adaptation; SAN, Stichting Afasie Nederland.

[1]Group sizes differ among measures due to missing data.

Supplementary Table 10.2 Percentage of patients with abnormal performance on neglect measures, administered during the neglect screening (*N* = 70).

Task	% patients with abnormal performance at neglect screening
CBS only	28.6
SC only	0
LB only	1.4
CBS and SC	18.6
CBS and LB	12.9
SC and LB	1.4
CBS, SC and LB	37.1

Abbreviations: CBS, Catherine Bergego Scale; LB, line bisection task; SC, shape cancellation task.

Supplementary Table 10.3 Fixed-effect predictors and covariates for predicting the CBS across week 1 to 6, including patients with neglect at baseline (CBS ≥ 7) and right hemispherical damage (*n* = 42).

Predictor	β	SE_β	95% CI	*p*
Group (PA)[1]	1.77	1.58	-1.36 to 4.89	.265
Time	-0.59	0.22	-1.04 to -0.14	.009
Time * Group	-0.35	0.32	-0.98 to 0.29	.281
Baseline CBS	0.85	0.11	0.63 to 1.06	< .001
Days post-stroke	0.04	0.02	0.00 to 0.07	.049
Gender (male)	-2.22	1.28	-4.81 to 0.36	.090

Note. *n* = 21 in the PA group, *n* = 21 in the SA group.

Abbreviations: CBS, Catherine Bergego Scale, PA, prism adaptation; SA, sham adaptation.

[1]The Beta coefficient for the predictor 'Group' indicates that the predicted CBS score is on average 1.77 points higher for the PA group compared to the SA group, although this effect is not significant.

Supplementary Table 10.4 Fixed-effect predictors and covariates for predicting the CBS across week 1 to 6, including the variable aftereffect instead of group (*n* = 69).

Predictor	β	SE_β	95% CI	*p*
Aftereffect in mm	0.03	0.03	-0.03 to 0.09	.287
Time	-0.68	0.11	-0.91 to -0.46	< .001
Baseline CBS	0.74	0.06	0.62 to 0.87	< .001
Days post-stroke	0.03	0.02	0.00 to 0.06	.027
Gender (male)	-1.79	0.96	-3.71 to 0.13	.068

Abbreviation: CBS, Catherine Bergego Scale.

Supplementary Table 10.5 **Fixed-effect predictors and covariates for predicting the MAC asymmetry score across week 2, 4 and 14, including patients with neglect at baseline (asymmetry score ≥ 3) and right hemispherical damage (*n* = 35).**

Predictor	β	SE_{β}	95% CI	*p*
Group (PA)[1]	0.15	0.84	-1.52 to 1.83	.856
Time	-0.16	0.05	-0.27 to -0.05	.005
Time * Group	-0.04	0.09	-0.22 to 0.14	.660
Baseline MAC	0.58	0.14	0.30 to 0.86	< .001

Note. *N* = 15 in the PA group, *N* = 20 in the SA group.

Abbreviations: MAC, Mobility Assessment Course, PA, prism adaptation; SA, sham adaptation.

[1]The Beta coefficient for the predictor ‘Group’ indicates that the predicted MAC asymmetry score is on average 0.15 points higher for the PA group compared to the SA group, although this effect is not significant.

Supplementary Table 10.6 **Fixed-effect predictors and covariates for predicting the MAC asymmetry score across week 2, 4 and 14, including the variable aftereffect instead of group (*n* = 69).**

Predictor	β	SE_{β}	95% CI	*p*
Aftereffect in mm	-0.01	0.01	-0.04 to 0.02	.539
Time	-0.13	0.03	-0.18 to -0.07	< .001
Baseline MAC	0.65	0.06	0.53 to 0.77	< .001

Abbreviation: MAC, Mobility Assessment Course.

Supplementary Table 10.7 **Fixed-effect predictors and covariates for predicting the SC asymmetry score across week 1 to 14, including patients with neglect at baseline (asymmetry score ≥ 4) and right hemispherical damage (*n* = 26).**

Predictor	β	SE_{β}	95% CI	*p*
Group (PA)[1]	-0.13	2.41	-5.01 to 4.75	.958
Time	-0.51	0.13	-0.77 to -0.24	< .001
Time * Group	0.12	0.23	-0.34 to 0.57	.605
Baseline SC	0.30	0.16	-0.03 to 0.64	.075

Note. *n* = 12 in the PA group, *n* = 14 in the SA group.

Abbreviations: PA, prism adaptation; SA, sham adaptation; SC, shape cancellation task.

[1]The Beta coefficient for the predictor ‘Group’ indicates that the predicted SC asymmetry score is on average 0.13 points lower for the PA group compared to the SA group, although this effect is not significant.

Supplementary Table 10.8 Fixed-effect predictors and covariates for predicting the SC asymmetry score across week 1 to 14, including the variable aftereffect instead of group (*n* = 69).

Predictor	β	SE_{β}	95% CI	*p*
Aftereffect in mm	0.02	0.03	-0.04 to 0.07	.519
Time	-0.20	0.05	-0.29 to -0.11	< .001
Baseline SC	0.49	0.06	0.38 to 0.61	< .001

Abbreviation: SC, shape cancellation task.

Chapter 11

Summary and general discussion

The general objective of this thesis was to better understand and treat neglect, a frequent and disabling disorder after stroke. To this aim I addressed three themes within the field of neglect rehabilitation: neglect subtypes, sensitive and dynamic diagnosis of neglect, and prism adaptation as a potential treatment for neglect. In the following paragraphs, I will summarize the main findings, discuss some theoretical considerations, and make suggestions for future research and clinical practice.

Summary of main findings

Part I: Neglect subtypes

In neglect research, mostly patients with left-sided neglect following right hemisphere stroke are included. Knowledge regarding neglect is, therefore, mainly based on a subset of patients. This is unfortunate, however, as right-sided neglect also occurs frequent, and it is unknown whether knowledge regarding diagnosis, treatment, and consequences in ADL is generalizable to this patient group. Our retrospective observational study that was described in **Chapter 2** (N = 335), confirmed that left- and right-sided neglect are both common in the subacute phase post-stroke onset (i.e., approximately 1 month post-stroke onset, 16% of stroke patients admitted to inpatient rehabilitation showed left-sided neglect and 9% showed right-sided neglect). The lateralized attentional deficit was more severe in patients with left-sided compared to patients with right-sided neglect, as measured with cancellation and bisection tasks, and based on observations in ADL. The consequences in other domains, however, were largely comparable: compared to patients without neglect, both patients with left- and right-sided neglect were less independent in mobility and self-care at admission to rehabilitation and at discharge. It is, therefore, of great importance to adequately diagnose and treat both left- and right-sided neglect. In addition, scientific research focusing on diagnosis, treatment and general knowledge on the disorder should include all neglect patients. For the current thesis, we included patients with left- and right-sided neglect in all of our studies. We compared these groups, for example, regarding search organization, and found that neglect patients with right brain damage searched less organized compared to neglect patients with left brain damage (**Chapter 5**). As the degree of disorganized search related to the severity of neglect, and neglect is more severe after right than left brain damage, this could explain the observed differences.

In **Chapter 3**, we focused on neglect for different regions of space. Studies in animals and healthy participants suggest that different brain regions are involved in the processing of visuospatial information in peripersonal space versus extrapersonal space. Lesions in these different areas could, therefore, lead to attentional disorders in one or both regions of space. Prior studies showed that visual attention can, indeed, be affected specifically for one region of space. In 98 to 129 stroke patients, we studied neural substrates of region-specific neglect, based on a shape cancellation and line bisection task respectively. We found that several right temporal and thalamic regions were related to both peripersonal and extrapersonal neglect, and several additional right temporal, parietal and occipital regions were only related to extrapersonal neglect. None of the brain regions were *only* related to peripersonal neglect. It seems that mostly *shared* anatomical regions are related to peripersonal and extrapersonal neglect.

Defining and studying subtypes of neglect

Neglect is a complex and heterogeneous disorder, consisting of spatial deficits, such as impaired spatial working memory (Malhotra et al., 2005), and non-spatial deficits, such as impairments in arousal (Corbetta & Shulman, 2011). The core cognitive deficit is lateralized inattention. Visuospatial attention is, however, not a single process, and its components may be individually subject to disruption, contributing to the different manifestations of neglect (Carter et al., 2017; Rode, Pagliari, Huchon, Rossetti, & Pisella, 2017). A distinction can be made, for example, between a 'where' spatial deficit, relating to difficulty with contralesional perceptual awareness, and an 'aiming' spatial deficit, relating to disturbed spatial action planning and execution (Barrett et al., 2012; Goedert et al., 2014; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Neglect could be present in different regions of space (**Chapter 3**) or different frames of reference (egocentric or allocentric; Verdon et al., 2010). Another distinction can be made between patients who are impaired in the selective, goal-driven allocation of attention or patients who are impaired in automatic, stimulus-driven allocation of attention (Carter et al., 2017).

As a consequence of these different manifestations, there is an ongoing debate about the proper terminology for visuospatial neglect. In the absence of an undisputed golden standard, it remains open whether abnormal performance on a cancellation task, asymmetrical target detection during the Mobility Assessment Course, clinical observations of neglect behaviour in ADL, or a combination of such aspects should be diagnosed as "neglect". Different tasks for neglect rely on different skills and different underlying anatomical substrates. Better use of (clear) terminology for the type of lateralized inattention is needed to enhance clarity on the specificity of impairments in patients, both in science and clinical practice. Specific terms should therefore be used in addition to the more general term "neglect", or it should be clearly specified what is meant by it. Administering multiple tasks that target different aspects of neglect is necessary to gain knowledge on how subtypes relate to each other regarding frequency, severity, and consequences in ADL. Eventually, this could improve assessment and treatment of patients.

Part II: Sensitive diagnosis of neglect

In this thesis I described some advantages and disadvantages of the current paper-and-pencil method for diagnosis of neglect. The first important drawback is that not all subtypes of neglect are assessed, for example extrapersonal neglect. Second, the current diagnosis of neglect lacks sensitivity. In order to solve this issue, we need: 1) measures on the level of ADL, 2) sensitive multitasks, and 3) detailed measures of the attentional deficit.

Measures on the level of ADL

Discrepancies exist between performance on paper-and-pencil tasks and patient functioning in daily life. This is problematic for accurate diagnosis of neglect and for proper evaluation of rehabilitation interventions. A direct solution to measure neglect on the level of ADL is the use of a structured observation scale, such as the Catherine Bergego Scale (Azouvi et al., 1996), which we validated in a Dutch rehabilitation setting (Ten Brink et al., 2013). The Catherine Bergego Scale is an ecological valid task in which behaviour is observed in several relevant daily life situations and, therefore, a useful addition to current diagnostics. Using this observation scale is, however, not sufficient, as multitasking is not explicitly assessed. In addition, during rehabilitation, in particular daily life situations are trained, and the use of compensatory strategies could mask the presence of an attentional deficit. Applying compensatory strategies is, of course, a goal of rehabilitation, but in some situations it is useful to objectify whether an attentional deficit is (still) present in situations in which conscious strategies are difficult to apply, as these match real daily life situations (such as traffic or work) more accurate.

Sensitive multitasks

Several multitasks have been developed to assess neglect in a more sensitive manner. Preferably, one of the following aspects is taken into account: (moving) interference of other stimuli, time pressure (i.e., stimuli are visible for a limited period of time or reaction time is measured; Rengachary et al., 2009), and performing multiple actions at the same time (van Kessel et al., 2013). Virtual reality simulations are suitable for such tasks (see Spreij et al., 2017; Verheul et al., 2016 for an overview of the use of virtual reality in cognitive rehabilitation). An example is the driving simulation task of van Kessel and colleagues (2013), during which stimuli have to be detected while driving. Such tasks - especially in a daily setting - add to the current diagnosis (Marshall et al., 1997; Spreij, Ten Brink, Visser-Meily, & Nijboer, in revision; van Kessel et al., 2013). At this moment, many of these computer tasks are not being used in the clinical practice. It is, however, important to objectify the lateralized attentional deficit in a setting that encompasses the attentional load of daily life, otherwise, in some patients neglect will be underdiagnosed. In **Chapter 4**, we evaluated a dynamic multitask to assess neglect in a sensitive manner: the Mobility Assessment Course. We assessed 113 subacute stroke patients and 47 healthy subjects with the Mobility Assessment Course. An association existed between performance on the Mobility Assessment Course and performance on standard paper-and-pencil neglect tasks, although double dissociations were also found. Especially patients who were part of the 'recovered' group (based on the paper-and-pencil tasks) missed targets on their contralesional side during the Mobility Assessment Course. This fits the hypothesis that neuropsychological assessment is not always sensitive to detect neglect, and the Mobility Assessment Course may detect neglect in patients who do not show neglect during standard paper-and-pencil tasks. An additional benefit is that the use of a dynamic multitask aids the detection of right-sided neglect, as multitasking uncovers right-sided neglect better than static paper-and-pencil tasks in which patients can focus on one goal (Blini et al., 2016). Furthermore, the Mobility Assessment Course could be of value in providing insight to the patient. This final argument became clear to me while assessing the Mobility Assessment Course in neglect patients. During the pilot phase, for example, one patient could hardly believe me when (after assessment of the Mobility Assessment Course) I revealed to him how many targets were present on the left side (twelve), and how many targets he had found (six). When I left, he independently walked the route again, and still was not able to find all twelve targets. Only when he walked the route in the opposite direction, he found all twelve targets, which were on his right side now. When I came back to remove the targets, he told me this experience was an eye opener and he was a bit shocked, as he had not realized the severity of his neglect. This anecdote is not unique. During the RCT, multiple patients were especially triggered by the results of this task, and much less by the results of paper-and-pencil tasks. Apparently, when patients miss targets in the hallway - while consciously trying to find them -, they can relate this deficit more easy to daily life situations (such as traffic) compared to missing targets on a sheet of paper. An experience like that could, therefore, enhance insight. We conclude that this task can already be used next to standard neuropsychological assessment.

Detailed measures of the attentional deficit

Finally, it is important to obtain detailed information on the attentional deficit. Although this seems to contradict with the statement to use measures on the level of ADL or ecological valid measures, it is useful to additionally gain information regarding the underlying processes that cause the eventual outcome. Thus, measures on the level of ADL and measures on the level of function are complementary, and together form the complete picture of attentional deficits in a given patient. Examples of such (experimental) tasks are cueing tasks or Temporal Order Judgement (Van der Stigchel & Nijboer, 2017), which could be used to derive more 'pure' measures of the attentional bias.

Next to the attentional bias, other cognitive processes that may relate to attention can be evaluated in more detail with digitized testing, such as search organization, involved in many daily processes and often disturbed after stroke. In **Chapter 5**, we aimed to investigate the relation between neglect and disorganized search. Based on performance on a cancellation task of 280 stroke patients and 37 healthy control subjects, we computed several measures to depict search organization. For example, we evaluated whether stroke patients used a systematic search pattern while finding targets, or whether an efficient search path was used (i.e., the shortest distance between consecutive cancelled targets). The intersections rate (i.e., the number of path crossings between consecutive cancelled targets) was the most sensitive measure to depict disorganized search in a stroke population. It appeared that disorganized search is in particular related to neglect and is even more evident in severe neglect, which is related to right brain damage. In order to unravel the precise neural substrates of search organization, we studied CT and MRI scans of 78 stroke patients and performed voxel-based lesion-symptom mapping analyses in **Chapter 6**. The results confirmed the right-hemispherical dominance for search organization. Specific brain areas that were related to disorganized search were the right lateral occipital cortex, superior parietal lobule, postcentral gyrus, superior temporal gyrus, middle temporal gyrus, supramarginal gyrus, inferior longitudinal fasciculus, first branch of the superior longitudinal fasciculus, and the inferior fronto-occipital fasciculus. These areas have been related to conjunctive search and spatial working memory in prior research. This might suggest that search organization during cancellation is related to lower-order visuospatial processing instead of, for example, higher-order executive functioning, although more studies are needed to confirm this hypothesis. In **Chapter 7**, we investigated more thoroughly whether search organization is related to one of the cognitive domains that are usually assessed during neuropsychological testing. 439 Stroke patients performed a shape cancellation task, and measures of search organization were computed. In addition, we collected data on a range of neuropsychological tasks, measuring neglect, visuospatial perception and construction, psychomotor speed, executive functioning/working memory, spatial planning, rule learning, short-term auditory memory, and verbal working memory. We performed exploratory factor analyses to explore underlying cognitive domains. Four clusters were separated: “Executive functioning”, “Verbal memory”, “Search organization,” and “Neglect”. Based on these results, search organization seems a distinct cognitive construct than the ones that are usually tested during neuropsychological assessment.

To summarize, neuropsychological tasks are increasingly being digitized. This provides access to more detailed measures and more dynamic measures for cognition. Administering cancellation tasks and analysing measures of search, for example, provides useful additional insights into the lower-order visuospatial processes of stroke patients. Although disorganized search is related to neglect, this is only a weak relation, and it might be a separate cognitive construct. With digitized neuropsychological testing, measures of search can nowadays easily be extracted.

Part III: Prism adaptation in the rehabilitation of neglect

In **Chapter 8**, we reviewed the literature to evaluate whether prism adaptation affects visual search in patients with neglect and which aspects of visual search behaviour are the most sensitive for the effects of prism adaptation. In most studies, only omissions or hits that were made on cancellation tasks were taken into account when the effects of prism adaptation were evaluated. An overall improvement was found on these measures following treatment with prism adaptation. In addition, less perseverations were made following prism adaptation. We concluded that there seems to be an overall effect of prism adaptation on finding targets, although specific search measures (e.g., regarding search organization) were not included. In **Chapter 9** and **10**, the study protocol and results of the RCT PAiR were described. Both patient groups (i.e., receiving sham adaptation and prism adaptation) improved on dynamic and static outcome measures of neglect. However, no differences were seen between groups. One of the main reasons for the neutral results could relate to the heterogeneity of the disorder, enhanced by the spontaneous neurobiological recovery in especially the subacute phase post-stroke onset or standard treatment effects (care as usual). They could have overshadowed the potential effects of prism adaptation. It must, however, be noted that RCTs (including sham adaptation as a control treatment) in the chronic phase or in mixed phases, included small patient groups (N = 11 to 22 in total) and no measures on the level of ADL (Angeli et al., 2004; Làdavas et al., 2011; Mancuso et al., 2012; Rossetti et al., 1998; Serino et al., 2009; Vangkilde & Habekost, 2010). Since most high-quality, large studies have been conducted in the subacute phase, this could be a reason for the predominant neutral results when comparing with smaller studies in later phases. Possibly, there are no beneficial effects of prism adaptation on neglect for most patients. Thus, based on the current evidence, we are not convinced prism adaptation should standardly be provided as a treatment for neglect.

What would be, then, the best approach for neglect treatment? We recently reviewed the literature, and found a comparable amount of evidence regarding alleviation of neglect for visual scanning training, prism adaptation, and limb activation training. Unfortunately, none of the treatments has been proven to be effective on the long-term or as measured with measures on the level of ADL (Ten Brink, van Kessel, et al., 2017). A reason for neutral RCTs regarding neglect treatment regards the heterogeneity of the disorder itself. There is consensus that, for example, prism adaptation might not affect all neglect components, in all patients, in - if even possible - comparable manner. Neglect treatments can roughly be divided in passive versus active therapies, restorative versus compensatory therapies and top-down versus bottom-up therapies (Saevarsson et al., 2011). Prism adaptation is considered a bottom-up, active restorative intervention, in contrast with, for example, visual scanning training, which is considered a top-down, active compensatory therapy. Theoretically, it should be most efficient to pick a single therapy based on the patient's symptoms. In patients with impaired automatic attention, for example, top-down compensatory strategies that are taught during visual scanning training would probably not improve allocating attention to fast and unexpected events, such as those occurring in traffic. These patients could perform well on a static paper-and-pencil task without time pressure, but show asymmetric response times on a dynamic computer task. A bottom-up treatment, such as brain stimulation, could be more effective to reduce this attentional asymmetry. It must be noted, though, that this is speculative and, currently, no evidence exists for this specific example. At this point we can, therefore, not recommend one treatment over others. Preferably, several treatments are combined in a given patient as combinations of treatments seem to work best (either parallel or sequentially; Saevarsson et al., 2011). Although we do not know yet what underlying mechanisms are, different treatments possibly affect different aspects of neglect within one patient, or treatments could potentially interact with each other in a positive manner.

Implications for research and clinical practice

Future research

Cognition has been labelled as the number one priority to allocate research resources among people affected by stroke (Pollock et al., 2012). Future research should, therefore, keep focusing on the diagnosis and treatment of cognitive disorders such as neglect. Many neutral RCTs on neglect treatment have been published over the years, or only small beneficial treatment effects have been found (Azouvi, Jacquin-Courtois, & Luauté; Bowen et al., 2013; Fasotti & van Kessel, 2013; Kerkhoff & Schenk, 2012). Focusing on precise diagnosis of neglect subtypes and evaluating their responsiveness to a certain treatment is, therefore, urgently needed. As a wide range of tasks is used between studies to select patients for research, conclusions regarding, for example, neural substrates or treatment effects are not comparable. Thus, consensus should be reached regarding a standard set of tasks to measure neglect (as is also specified for general rehabilitation outcome measures, see Kwakkel et al., 2017). At least, information on the exact inclusion criteria (e.g., tasks and thresholds used to define neglect) should be described in more detail.

Studies on neglect treatment should focus on large groups of patients with a specific subtype of neglect. This is, however, hardly possible in a standard rehabilitation setting in the Netherlands. In order to conduct group studies on the different subtypes, therefore, (European) collaborations are necessary. At the same time, perhaps we have to take a step back, and conduct smaller (case) studies first, to understand the mechanisms of neglect treatments better, especially in relation to specific patient characteristics, such as the lesion location or brain functioning. For example, beneficial effects of prism adaptation in neglect patients are related to a modulation of brain regions that are important in spatial attention and visuo-motor behaviour (Chen et al., 2014; Newport, Brown, Husain, Mort, & Jackson, 2006; Saj et al., 2013). A relative sparing of these brain areas might be needed for beneficial effects of prism adaptation on neglect (Saj et al., 2013). Furthermore, possibly, neglect patients who do not show spontaneous neurobiological recovery – or only to a limited extent – respond better to treatment compared to patients who do show spontaneous neurobiological recovery. Being able to predict recovery patterns would, therefore, be highly relevant regarding the development of neglect treatments. At this moment, we are determining which recovery trajectories can be dissociated in our sample of neglect patients and which patient properties relate to the different recovery groups.

Research regarding the development of new diagnostic measures on the level of ADL should focus on dynamic (multi)tasks that preferably resemble daily life situations. Virtual Reality simulations could be used to evaluate neglect in a standardized, ecologically valid, dynamic manner. Techniques that allow patients to walk or drive with their wheelchair while performing a task are especially promising in the development of multitasks. On the level of function, a promising method is the evaluation of eye movements, closely related to attention. It is known that in neglect patients, eye movements are disturbed during reading (Primativo et al., 2015), visual search (Behrmann, Watt, Black, & Barton, 1997) and free exploration of a scene (Müri, Cazzoli, Nyffeler, & Pflugshaupt, 2009). It is, however, questioned whether the presumed tight relationship between eye movements and attention is present in brain-damaged patients. Case studies have shown that, despite some patients do fixate a certain target, the visual information is not sufficiently processed and does not reach conscious awareness (Benson, Ietswaart, & Milner, 2012; Khan et al., 2009). Measuring eye movements could provide the neuropsychologists with more detailed information on whether a patient shows problem with ‘looking’ versus ‘seeing’.

Finally, fundamental knowledge regarding brain mechanisms of attention could improve our understanding of neglect subtypes. In this thesis I describe several studies regarding lesion locations and lesion overlay, although it should be noted that focal lesions have remote effects on the function of distant brain regions via networks (Carey et al., 2013). Stroke severity is determined by both lesion volume and lesion location. Lesions in, for example, white matter tracts can have more severe consequences than cortical lesions. It is, nowadays, clear that impairment after stroke results from changes in the overall network rather than from a single lesioned area (Carey et al., 2013). Lesion overlay studies are a first step to gain insight into the potentially affected brain areas related to neglect subtypes and treatment responsiveness. In the future, research should focus on the white matter tracts and (the condition of) brain networks (among other innovative neuroscience measures).

Clinical implications

So, how can we use the current knowledge about neglect to improve todays neglect rehabilitation? First of all, diagnosis of neglect could be improved by balancing function specific tasks and dynamic dual tasks. As there is no golden standard to assess neglect, the general opinion is that multiple tasks should be administered. Due to limited resources and limited load-bearing capacity of the patient, however, a selection of tasks has to be made. Function specific tasks (in which the lateralized attentional disorder is examined as precise as possible) and tasks that accurately measure the presence and severity of neglect in a dynamic setting, closer to the dynamics of daily life, should be balanced. An example of a test battery would be a computerized cancellation task, administered at two distances (peripersonal and extrapersonal space), a fast, dynamic computer task (such as a Temporal Order Judgment task; Van der Stigchel & Nijboer, 2017), a dynamic multitask (such as the Mobility Assessment Course or a driving simulation task), and finally, observations of neglect behaviour in ADL (e.g., using the Catherine Bergego Scale). In addition, specific information on attentional processes (e.g., the process of visual search) could easily be gained by digitizing neuropsychological assessment. As we have shown in **Chapter 5**, some patients without neglect search disorganized on a cancellation task while no targets are missed eventually. This information, combined with, for example, search time or starting position, could indicate the presence of a mild lateralized attentional deficit, which would have been missed when only the number of omissions was used to evaluate performance.

A second improvement of neglect rehabilitation regards psycho-education, based on knowledge regarding disturbed underlying attentional mechanisms. When more detailed knowledge is gained during the diagnostic process, a better explanation of certain behaviour could be provided. For example, differences between behaviour in a static test situation (with paper-and-pencil tasks) versus a dynamic daily life environment, can be explained based on the differences in attentional load or (visual) input. Furthermore, administering a dynamic task (such as the MAC) could be used to enhance insight. In addition, when a structured observation scale (e.g., CBS) has been administered, the item scores can be used to educate the patient about specific problems he or she might encounter in daily life. Explaining why patients face certain problems, and what underlying mechanisms are, is regarded as highly important in rehabilitation and aids patients and their families in the rehabilitation process.

Third, as none of the available treatments is proven to be the most effective, we recommend to continue with care as usual (i.e., visual scanning training). In addition, (neuro)psychologists should experiment with additional treatments for a given patient. The choice of treatment should be determined based on the level of insight, fatigue, motivation, and potential contraindications (e.g., no brain stimulation in epileptic patients or no neck vibration in patients with a pacemaker).

To conclude

The past years I have been introduced into the field of (cognitive) rehabilitation. Trained as an experimental neuropsychologist I greatly enjoyed contributing to patient care through research; using basic knowledge for solutions to issues in clinical practice. Translational research, i.e., exploiting theoretical knowledge from different disciplines to improve the healthcare system, is not new, and the premise in academic hospitals. Often, however, the translation of fundamental knowledge into clinical practice is insufficient, as translational research is not easy and requires to connect with a lot of people and parties. I had the opportunity to talk about our research with many practitioners, such as rehabilitation physicians, (neuro)psychologists, occupational therapists, physical therapists and speech therapists. Brainstorming about, for example, the rationale for experimental designs in diagnosis of neglect, the implementation of new tasks in a rehabilitation setting, the definition of neglect, and, of course, many practical issues (e.g., how to include patients with aphasia in our trial; a major gap in many studies), has provided me with valuable insights. In addition, I actively participated in the fields of experimental psychology and neuroscience, which encouraged me to critically review my research and keep up with the latest scientific developments. Such lines of communication are crucial when you are conducting research in a field that is in between fundamental and applied research, and allow not only to improve health care, but at the same time contribute to basic science. For future research, incorporating aspects of (cognitive) neuroscience, neuropsychology, neurology, imaging techniques and rehabilitation, is necessary to achieve real progress in both science and patient care. Proactive participation, communication, and collaboration with the different fields are key ingredients for effective translational research.

In this thesis, I have unravelled a little bit of the attentional disorder that is called “neglect”. I contributed to the basic knowledge on anatomy of attentional processes in the brain, regarding lateralization (**Chapter 2**), region-specificity (**Chapter 3**), and visual search (**Chapter 6**). In addition, by including measures that are relevant for clinical practice, we created more awareness among practitioners on the different subtypes of neglect, such as right-sided neglect (**Chapter 2**) and neglect in extrapersonal space (**Chapter 3**). Based on concerns of practitioners on task sensitivity of neuropsychological neglect tasks, we developed and studied dynamic, sensitive diagnostic measures for neglect (**Chapter 4**) and measures for attentional processes related to neglect (i.e., visual search, **Chapter 5 and 7**), which can – and are – already being used in clinical practice. Finally, a major request from clinical practice regards evidence on neglect treatment. The results of our RCT on prism adaptation (**Chapter 8** to **10**) contribute to the collection of data on this topic, and will aid practitioners in their decision making on the choice of treatment for patients with neglect.

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Samenvatting

Summary in Dutch

Ieder jaar krijgen in Nederland ongeveer 45.000 mensen een beroerte (cerebro vasculair accident; CVA), waarbij een deel van de hersenen tijdelijk geen zuurstof meer krijgt. Een beroerte is vaak ingrijpend en kan veel impact hebben op iemands leven. Meteen na de beroerte vallen de fysieke gevolgen, zoals het niet meer kunnen lopen, het meest op. Er zijn ook veranderingen in het denken, dat noemen we cognitieve gevolgen. Eén van de mogelijke cognitieve gevolgen is visueel neglect. Mensen met neglect negeren of ontkennen de helft van hun lichaam of een deel van de ruimte om hen heen, hoewel zij niet blind zijn. Dit kan leiden tot verschillende symptomen: mensen scheren maar één kant van hun gezicht, eten slechts de helft van hun bord leeg of merken bezoek dat aan de aangedane zijde zit niet op. Meestal is dit de zijde tegenovergesteld aan de kant waar het letsel in de hersenen is gelokaliseerd (de contralaterale zijde) en vaak aan dezelfde kant waar ook een verlamming aan de arm en het been is. Ondanks deze opvallende symptomen van verwaarlozing zijn veel mensen met neglect zich niet bewust van hun aandoening of rapporteren zelf geen klachten. Dit komt doordat neglect vaak gepaard gaat met een verstoord ziekte-inzicht. Neglect komt vlak na een beroerte bij ongeveer 30 tot 50% van de patiënten voor. De meerderheid van de patiënten met neglect herstelt spontaan binnen de eerste maanden. Echter, bij 40% van de patiënten met neglect is de stoornis een jaar later nog aanwezig. Patiënten met neglect revalideren minder snel en goed, en eenmaal thuis zijn zij minder zelfstandig dan patiënten zonder neglect. Een goede behandeling is dus van belang. Het doel van dit proefschrift is om neglect beter te begrijpen, beter te kunnen testen en vervolgens beter te kunnen behandelen.

Deel 1: Neglect subtypes

Neglect komt vaker voor, is ernstiger en blijft langer bestaan na beschadiging van de rechterhersenhelft dan na beschadiging van de linkerhersenhelft. In wetenschappelijke studies worden meestal alleen patiënten met linkszijdig neglect (na rechtszijdig hersenletsel) geïncludeerd. Kennis over neglect is daarom voornamelijk gebaseerd op deze patiëntgroep. Dit is jammer omdat rechtszijdig neglect ook regelmatig voorkomt en we niet weten of kennis over diagnostiek, behandeling en de gevolgen in het dagelijks leven zo één-op-één is over te nemen voor deze patiënten. In **Hoofdstuk 2** onderzochten we de verschillen en overeenkomsten tussen links- en rechtszijdig neglect in een groep van 335 patiënten. Deze patiënten waren na een beroerte opgenomen voor revalidatie. In onze groep had 16% van de patiënten linkszijdig- en 9% rechtszijdig neglect. Hoewel het neglect ernstiger was voor patiënten met linkszijdig neglect, waren zowel patiënten met links- als rechtszijdig neglect minder zelfstandig dan patiënten zonder neglect (en vergelijkbaar ten opzichte van elkaar). Het is daarom belangrijk om beide subtypes van neglect adequaat te diagnosticeren. Daarnaast zou wetenschappelijk onderzoek zich óók op beide subtypes moeten richten. In alle studies die ik in dit proefschrift beschrijf zijn zowel patiënten met links- als rechtszijdig neglect meegenomen.

Een bestaande hypothese is dat verschillende hersengebieden betrokken zijn bij het verwerken van visuele informatie in verschillende afstanden van de ruimte. Er kan een onderscheid worden gemaakt tussen de nabije ruimte (binnen armlengte) en de verre ruimte (buiten armlengte). Als het ene hersengebied betrokken is bij verwerking van visuele informatie in de nabije ruimte, en het andere hersengebied bij verwerking van informatie in de verre ruimte, zou beschadiging in één van deze twee hersengebieden mogelijk kunnen leiden tot neglect specifiek voor één van de afstanden. Om deze hypothese te toetsen bekeken we in **Hoofdstuk 3** hersenscans van 129 patiënten met een beroerte bij wie neglecttaken waren afgenomen in de nabije- en verre ruimte. We vonden een aantal hersengebieden die specifiek geassocieerd zijn met neglect in de verre ruimte. Daarnaast vonden we een paar hersengebieden die met neglect in zowel de nabije als in de verre ruimte zijn geassocieerd. Dit kan er op duiden dat bepaalde hersengebieden betrokken zijn bij het verwerken van visuele informatie in zowel de nabije als verre ruimte, en enkele gebieden alleen bij het verwerken van informatie in de verre ruimte. We hebben nu vooral gekeken naar de overlap in hersenbeschadigingen door alle scans als het ware op elkaar te leggen en te kijken welke gebieden het meest gerelateerd waren aan het hebben van neglect voor de nabije of verre ruimte. Inmiddels zijn er echter betere technieken en in vervolgonderzoek zou dan ook zeker met deze technieken gekeken kunnen worden of verschillende netwerken in de hersenen beschadigd zijn als mensen neglect in de nabije of juist de verre ruimte hebben.

Deel 2: Sensitieve diagnostiek van neglect

Om neglect vast te stellen worden meestal neuropsychologische pen-en-papiertaken gebruikt. De patiënt wordt bijvoorbeeld gevraagd bepaalde vormen weg te strepen tussen afleiders, of het midden van een lijn te markeren. Deze manier van testen heeft enkele nadelen: er kan op één doel gefocust worden, er is weinig afleiding tijdens de taken en er is geen tijdslimiet. In een dagelijkse situatie waar meer beweging is (bijvoorbeeld mensen die langs lopen), iemand zelf beweegt of meerdere dingen tegelijkertijd uitgevoerd moeten worden (zoals lopen en praten), wordt het aandachtsysteem meer belast. Hierdoor kan het zijn dat op basis van een pen-en-papiertaak geen neglect wordt vastgesteld, terwijl dit er wel is in dagelijkse situaties. Er is dus een discrepantie tussen de 'statische' testomgeving en het dynamische dagelijks leven. In **Hoofdstuk 4** onderzochten we of de Mobility Assessment Course (MAC), een dynamische multitaak, geschikt is om neglect vast te stellen. De MAC is een taak waarbij een route wordt uitgezet binnen de gangen van een revalidatiecentrum of ziekenhuis. Er worden gele vierkantjes (doelen) bevestigd aan de muren van de route. De patiënt wordt gevraagd om de route te lopen of met een rolstoel te rijden, en onderweg de doelen aan te wijzen. Omdat niet gestopt of omgekeerd mag worden is er geen ruimte voor compensatiestrategieën. We bekeken of het mogelijk was om de taak af te nemen bij revalidanten na een beroerte en wat de overeenstemming was met andere taken voor neglect. We vroegen 113 patiënten die met een beroerte waren opgenomen voor revalidatie om de route af te leggen en aan te geven waar de doelen zich bevonden. Daarnaast hebben 47 gezonde mensen (zonder neurologische aandoeningen) de taak afgerond. We vonden een relatie tussen prestatie op de MAC en prestatie op bestaande pen-en-papiertaken voor neglect, hoewel dubbele dissociaties (dat wil zeggen, mensen die uitvallen op de ene taak maar niet op de andere taak, en andersom) ook gezien werden. Opvallend was dat de meerderheid van de patiënten die twee weken vóór de MAC afname een afwijkende score lieten zien op een pen-en-papier taak, maar op de dag van MAC afname niet meer, wél uitviel op de MAC. Dit past bij de hypothese dat pen-en-papier taken niet altijd sensitief genoeg zijn om neglect vast te stellen, en dat met behulp van de MAC neglect kan worden vastgesteld bij patiënten die niet uitvallen op pen-en-papiertaken. De MAC kan op dit moment al gebruikt worden als aanvulling op een standaard neuropsychologisch onderzoek.

Zoals hierboven al geschreven, is een veelgebruikte pen-en-papiertaak voor neglect een wegstreeptaak waarbij doelen moeten worden gevonden tussen afleiders. Als er meer doelen worden gemist aan de ene kant van het papier dan aan de andere kant, is dit een indicatie voor neglect. Echter, er wordt meestal niet gemeten *hoe* iemand de taak uitvoert, bijvoorbeeld hoeveel tijd iemand nodig heeft, waar iemand begint met zoeken of hoe georganiseerd het zoeken verloopt. Uit observaties blijkt dat sommige patiënten alle doelen wel vinden maar hier lang over doen of een ongestructureerd zoekpatroon hanteren. Mogelijk geeft het zoekproces informatie over onderliggende cognitieve problemen. In **Hoofdstuk 5** onderzochten we de relatie tussen neglect en ongeorganiseerd zoeken. We bekeken zoekpatronen van 280 patiënten met een beroerte en 37 gezonde controles en berekenden verschillende maten om de mate van structuur bij visueel zoeken weer te geven. We bekeken bijvoorbeeld of het patroon systematisch (van links naar rechts, van onder naar boven of andersom) en efficiënt was (was er veel of weinig afstand tussen de opeenvolgend aangestreepte doelen?). Het aantal kruisingen van (denkbeeldige) lijnen tussen opeenvolgend weggestreepte doelen bleek de beste maat om de mate van zoekorganisatie in patiënten met een beroerte weer te geven. We vonden dat patiënten met neglect minder georganiseerd zochten en dat de mate van ongeorganiseerd zoeken samenhing met de beschadigde hersenhelft (de patiënten met rechtszijdig hersenletsel zochten minder georganiseerd dan de patiënten met linkszijdig hersenletsel) en de ernst van neglect, waarbij ernstiger neglect samenhing met een minder georganiseerd zoekpatroon.

In **Hoofdstuk 6** bekeken we welke hersengebieden betrokken zijn bij de mate van organisatie tijdens zoeken. We verzamelden hersenscans van 78 patiënten met een beroerte die een wegstreeptaak hadden gedaan en bekeken vervolgens de laesielocaties die zouden passen bij ongeorganiseerd zoeken. Uit de resultaten bleek dat vooral patiënten met beschadiging in de rechterhemisfeer ongeorganiseerd zochten. De gebieden binnen de rechterhemisfeer die betrokken waren bij zoekorganisatie kwamen overeen met gebieden die, in eerdere studies, in verband zijn gebracht met andere vormen van visueel zoeken en ruimtelijk werkgeheugen.

In **Hoofdstuk 7** bekeken we of zoekorganisatie gerelateerd is aan één van de cognitieve domeinen die normaal gesproken tijdens een neuropsychologisch onderzoek gemeten worden. We bekeken testgegevens van 439 patiënten met een beroerte, die zowel de wegstreeptaak hadden gedaan als een aantal standaard neuropsychologische taken. Met behulp van exploratieve factoranalyse konden we vier clusters onderscheiden: “Executief functioneren”, “Verbaal geheugen”, “Zoekorganisatie” en “Neglect”. Zoekorganisatie lijkt dus een apart cognitief construct, en lijkt niet op de cognitieve functies die getest worden met de taken die we bekeken in deze studie.

Concluderend kan rechtszijdig hersenletsel leiden tot ongeorganiseerd zoeken en zoeken patiënten met neglect vaker ongeorganiseerd dan patiënten zonder neglect, al is dit niet altijd het geval. Zoekorganisatie lijkt een aparte cognitieve functie naast executieve functies en verbaal geheugen, en is daarom belangrijk om mee te nemen in het neuropsychologische onderzoek.

Deel 3: Prisma adaptatie in revalidatie van neglect

De huidige behandeling voor neglect bestaat uit visuele scanningtraining. Tijdens deze behandeling worden compensatiestrategieën aangeleerd door patiënten te leren kijken naar de kant van het neglect. Een nadeel is dat deze behandeling zich alleen richt op compensatie, waarmee de stoornis zelf niet wordt behandeld. Een veel onderzochte behandeling is prisma adaptatie. Prisma adaptatie is erop gericht de verstoring in de ruimtelijke aandacht te herstellen. Tijdens een sessie prisma adaptatie dragen patiënten een prismabril, waardoor visuele informatie meer in de richting van de ipsilaterale zijde, dus de zijde tegenovergesteld van de neglectzijde, wordt waargenomen dan waar de informatie daadwerkelijk is. Patiënten worden gevraagd een groot aantal (ongeveer 100) snelle wijsbewegingen naar doelen te maken. In eerste instantie zal de optische verschuiving zorgen voor een afwijking van de wijsbeweging in de richting van de niet aangedane zijde ten opzichte van het doel. Door te mogen kijken naar de plek waar de vinger landt ten opzichte van het doel krijgt de patiënt visuele feedback over deze afwijking en zal hij of zij tijdens de volgende wijsbeweging motorische correcties maken in de richting van het doel. Als de bril wordt afgezet treedt er een zogenaamd na-effect op, waarbij de wijsbeweging afwijkt in de richting van de aangedane zijde. Het na-effect zou samenhangen met een al dan niet blijvende vermindering van neglect.

In **Hoofdstuk 8** bekeken we of in de literatuur bekend is welk effect prisma adaptatie heeft op visueel zoeken in patiënten met neglect. Na behandeling met prisma adaptatie misten patiënten met neglect tijdens wegstreeptaken minder doelen en streepten ze minder vaak doelen aan die ze eerder al hadden aangestreept (perseveraties). Er lijkt dus een positief effect te zijn van prisma adaptatie op het vinden van doelen. Echter, de meeste studies die we bekeken waren van lage methodologische kwaliteit en er waren geen specifieke zoekmaten meegenomen.

In **Hoofdstuk 9** en **Hoofdstuk 10** beschreven we het protocol en de resultaten van het gerandomiseerde effectonderzoek “Prisma Adaptatie in Revalidatie” (PAiR). In deze studie behandelden we 34 patiënten met neglect met prisma adaptatie en 35 met een placebobehandeling (sham adaptatie). De behandeling werd tussen 1 en 3 maanden na de beroerte gestart en duurde twee weken (10 minuten per dag). We onderzochten de patiënten op zeven momenten, tot 3 maanden na de behandeling. We vonden dat beide groepen vooruit gingen op onze statische en dynamische uitkomstmaten voor neglect. Echter, er werd geen verschil gemeten tussen de groepen. Patiënten met neglect herstelden dus niet sneller of beter na behandeling met prisma adaptatie vergeleken met sham adaptatie. Een van de belangrijkste redenen voor deze resultaten lijkt gerelateerd aan het moment van behandelen. Studies waarin geen effecten werden gevonden (zoals de onze) verschillen op dit punt van studies waarin wel effecten zijn gevonden. In de eerste maanden na de beroerte vindt in de hersenen veel spontaan neurobiologisch herstel plaats en een deel van de patiënten heeft na 3 maanden geen neglect meer. Ook kunnen patiënten verschillend reageren op, en profiteren van de huidige standaard compensatietraining voor neglect, waar onze deelnemers ook toegang tot hadden. Een groep patiënten met neglect in de vroege fase is dus heterogener dan een groep patiënten met neglect in de chronische fase, en effecten van spontaan neurobiologisch herstel of van de standaard neglecttraining zouden de meer subtiele effecten van prisma adaptatie kunnen hebben overschaduwd. Ten slotte zou het zo kunnen zijn dat prisma adaptatie niet werkt in de vroege fase vanwege de verschillende herstelprocessen die gaande zijn in de hersenen. Mogelijk moeten deze processen zijn gestabiliseerd voordat prisma adaptatie een gunstig effect op neglect kan hebben.

Tot slot

In **Hoofdstuk 11** bespreek ik de resultaten van de onderzoeken die zijn besproken in het proefschrift en doe ik aanbevelingen voor toekomstig onderzoek en de klinische praktijk. Het onderzoeken en behandelen van cognitieve gevolgen van een beroerte wordt als één van de belangrijkste prioriteiten gezien door mensen die zelf zijn getroffen door een beroerte. We moeten dus blijven nadenken over hoe we de diagnostiek en behandeling voor cognitieve stoornissen kunnen verbeteren. De afgelopen jaren is er veel onderzoek gedaan naar het behandelen van neglect. Helaas vonden maar weinig studies positieve effecten, of waren de effecten klein. Dit kan komen doordat neglect een heterogene stoornis is, waardoor waarschijnlijk niet elke patiënt baat heeft bij dezelfde behandeling. We zouden dus beter moeten uitzoeken welk subtype van neglect een patiënt heeft, en welke behandeling daar het meest effectief voor is. Om dit voor elkaar te krijgen zouden onderzoekers om te beginnen duidelijk moeten rapporteren welk type neglect zij hebben onderzocht. Om rekening te kunnen houden met verschillende subtypes zijn daarnaast ofwel grote studies nodig met veel patiënten, of moeten we een stap terug doen naar fundamenteel onderzoek waarbij kleine, homogene patiëntgroepen worden onderzocht. Zo komen we meer te weten over onderliggende mechanismes van verschillende subtypes, wat kan bijdragen aan het ontwikkelen van effectieve behandelingen. Het bestuderen van de anatomische basis van neglect subtypes draagt hier ook aan bij, waarbij we ons meer moeten richten op de neurale netwerken in plaats van alleen op hersengebieden. Dit is belangrijk omdat hersenbeschadigingen op lokaal niveau neurale processen in het gehele brein kunnen verstoren. Als we in patiënten met (subtypes van) neglect onderzoeken welke hersengebieden beschadigd zijn, in combinatie met welke netwerken verstoord zijn, hebben we een completer beeld van de onderliggende mechanismes van aandacht. Tenslotte zouden onderzoekers zich moeten blijven richten op het verbeteren van de diagnostiek van neglect. Op functieniveau kunnen verbeterslagen worden gemaakt door bijvoorbeeld oogbewegingen mee te nemen als een preciezere maat voor aandacht. Op activiteitenniveau zou meer gefocust kunnen worden op dynamische (multi)taken, die bij voorkeur een situatie uit het dagelijks leven simuleren.

Hoe kunnen we de kennis uit dit proefschrift inzetten om de revalidatie van neglect vandaag de dag te verbeteren? Ten eerste zou de diagnostiek van neglect verbeterd kunnen worden door zowel tests af te nemen die op functieniveau meten als tests en observatielijsten die op activiteitenniveau meten. Idealiter worden zowel statische (bijvoorbeeld een wegstreeptaak) als dynamische tests (bijvoorbeeld de MAC) afgenomen. Wanneer neuropsychologische tests digitaal worden afgenomen kunnen gemakkelijk aanvullende maten worden berekend (zoals maten voor zoekorganisatie) om een completer beeld de krijgen van de cognitieve functies. Ten tweede kan, indien de diagnostiek verbetert, beter worden uitgelegd aan de patiënt en zijn of haar naasten welke aandachtmechanismen verstoord zijn (psycho-educatie). Uitleg geven over waarom patiënten tegen bepaalde dingen aanlopen is een zeer belangrijk onderdeel van de revalidatie en helpt patiënten en hun naasten in het revalidatieproces. Tenslotte, aangezien geen van de beschikbare neglectbehandelingen voldoende bewezen effectief is, raad ik aan om de standaard neglectbehandeling (visuele scanningstraining) te blijven aanbieden. Daarnaast zouden neuropsychologen, bij voorkeur in samenwerking met onderzoekers, kunnen experimenteren met aanvullende behandelingen voor neglect.

In de afgelopen jaren heb ik kennis gemaakt met de cognitieve revalidatie. Als experimenteel neuropsycholoog heb ik met veel plezier translationeel en fundamenteel onderzoek uitgevoerd. Bij translationeel onderzoek wordt kennis uit fundamenteel onderzoek gebruikt om de patiëntenzorg te verbeteren. Het doen van translationeel onderzoek is niet nieuw, en geldt als uitgangspunt bij onderzoek in academische ziekenhuizen. Echter de kennis uit fundamenteel onderzoek wordt nog niet altijd voldoende benut in onderzoek naar de dagelijkse zorgtoepassing; het vergt veel samenwerking tussen verschillende mensen en partijen. Ik kon het translationeel onderzoek uitvoeren omdat ik de mogelijkheid had om samen te werken en te praten met artsen, psychologen en therapeuten uit de praktijk. Daarnaast bleef ik betrokken bij fundamenteel onderzoek in het veld van experimentele psychologie en het veld van neurowetenschappen door het overleg op de universiteit. Met de resultaten uit beide vormen van onderzoek, samengevat in dit proefschrift, is weer een kleine stap gezet in het verder ontrafelen van de aandachtstoornis die "neglect" wordt genoemd en in het verbeteren van diagnostiek en behandeling van patiënten met neglect.

Dankwoord

Onderzoek doe je niet alleen. Veel mensen hebben bijgedragen aan de studies in dit proefschrift, waarvoor dank. Er zijn een aantal mensen die ik in het bijzonder wil bedanken.

Prof. Dr. Visser-Meily, beste Anne. Ik wil je enorm bedanken voor je goede begeleiding en betrokkenheid. Ik waardeer je efficiëntie, je constructieve houding en vooral je bijdrage als revalidatiearts. Je hebt een duidelijke visie op patiëntenzorg en hoe onderzoek daarin kan bijdragen. Daar heb ik meer van geleerd dan ik vooraf misschien had gedacht en neem ik zeker met me mee in mijn verdere loopbaan.

Dr. Nijboer, beste Tanja. Wat heb ik veel van jou geleerd. Ik had me geen betere copromotor kunnen wensen. Je hebt me precies op de juiste manier uitgedaagd, door veel van me te vragen maar vooral ook heel veel terug te geven. Inhoudelijk heb je een grote rol gespeeld in dit traject, waar ik je in het bijzonder voor wil bedanken. Ik heb veel opgestoken van jouw kijk op de neuropsychologie, theoretische kennis en schrijfvaardigheid. Ik heb bewondering voor de studies die je allemaal weet op te zetten en het tempo waarin je dit doet. Je hebt een geweldige onderzoeksgroep om je heen en ik ben blij dat ik daar de afgelopen jaren deel van mocht uitmaken.

Het opzetten en uitvoeren van de PAiR studie werd door vele mensen in De Hoogstraat gedragen: secretaresses (Michele en Birsen), planners, fysiotherapeuten, ergotherapeuten, logopedisten, verpleegkundigen, psychologen, arts-assistenten, artsen, directie en medewerkers van de technische dienst. Ik wil iedereen bedanken voor hun essentiële rol in dit onderzoek. Ik heb De Hoogstraat leren kennen als een gastvrije plek voor onderzoekers. In het bijzonder wil ik Anja, Mirjam, Janet, Lara en Renée bedanken. Voor het laten slagen van PAiR was het cruciaal om steun te hebben vanuit de verschillende disciplines. Ook wil ik de verpleegkundigen, ergotherapeuten en fysiotherapeuten bedanken voor het invullen van maar liefst 1470 (!) observatielijsten.

De revalidanten en controleproefpersonen die hebben meegedaan aan ons onderzoek ben ik zeer dankbaar, zonder hun vrijwillige inzet had dit proefschrift er niet gelegen. Speciale dank gaat uit naar alle revalidanten die hebben meegedaan met PAiR. Het was een intensieve studie maar desondanks bleef iedereen trouw naar de behandelsessies en metingen komen.

Via deze weg wil ik het Revalidatiefonds bedanken voor de subsidie die dit project mede mogelijk heeft gemaakt.

Merel, Roemi, Marit, Inge, Sanne en Irene, jullie hebben geweldig werk verzet. Samen hebben we zo'n 600 meetsessies en 690 behandelsessies uitgevoerd. Stuk voor stuk waren jullie enthousiast en betrokken bij het project. Ik wil jullie enorm bedanken voor jullie bijdrage, zonder jullie was het niet gelukt!

Mijn collega's in het kenniscentrum: de senioronderzoekers, Andrie, Carlijn, Nienke en alle studenten wil ik bedanken voor de fijne sfeer in De Hoogstraat. Prof. Dr. Post, Marcel, bedankt voor de goede samenwerking bij het USER project en de kans die ik kreeg om daar een bijdrage aan te leveren. De junioren! Toen ik net begon Anne, Annerieke, Hileen, Martin, Matagne, Mattijs, Michiel, Nienke, en later in het traject Astrid, Carlijn, Chantal, David, Eline, Eline, Elsemieke, Jessica, Joris, Joris, Karen, Leonhard, Lies, Sophie, Tijn, Vincent en niet te vergeten Hubert; ik heb een fantastische tijd gehad in het kenniscentrum. Wandelingen (al dan niet in het kader van competitie om de meeste stappen), vrijmibo's, bridge-the-gap-bo's en juniorenuitjes. Ik ging iedere dag met veel plezier naar De Hoogstraat, daar hebben jullie zeker aan bijgedragen. Maremka, onze projecten liepen synchroon waardoor we, onder het genot van een biertje, altijd wat te bespreken hadden. Bedankt voor de leuke tijd samen!

Lauriane, paranimf, ik was blij toen jij na je onderzoeksstage bij ons in de onderzoeksgroep bleef. Je doet fantastisch onderzoek en het is heerlijk om met jou te kunnen sparren over eigenlijk alles. Dank voor de gezelligheid tijdens de vele lunches, treinreizen en congressen. Ik vind het een eer dat je me bij staat tijdens de verdediging!

Dr. Van der Stigchel, beste Stefan. Tijdens mijn stage bij jou en Tanja kwam ik er achter hoe leuk het is om wetenschappelijk onderzoek te doen. Nu, een paar jaar later, werken we opnieuw samen en kan ik bij jou onderzoek blijven doen naar aandachtsprocessen en hoe deze verstoord kunnen raken. Dank voor het vertrouwen dat je me hebt gegeven in mijn vaardigheden als onderzoeker.

Mijn nieuwe collega's van AttentionLab, eindelijk ben ik geen *external member* meer! Bedankt dat ik de afgelopen jaren mee mocht draaien met de labmeetings. Jessica, dank voor je bijdrage aan mijn allereerste experiment, waarbij ik je opstelling mocht gebruiken en je me participanten aanleverde. Nathan, bedankt voor je adviezen en altijd nuttige feedback. Martijn, dank voor je statistische hulp. Jasper, dank voor je Matlabhulp, zelfs vanuit Italië. Joris, het is fijn om een collega te hebben die ook heen en weer pendelt tussen De Hoogstraat en de UU (al dan niet met spullen van mij in de auto), leuk dat we blijven samen werken. Ook andere collega's bij de UU wil ik bedanken voor de warme ontvangst en goede sfeer.

Ik wil alle coauteurs en andere mensen met wie ik de afgelopen jaren heb mogen samenwerken bedanken. Edwin, bedankt voor je Pythonhulp tijdens mijn onderzoeksstage. Quirien, wat was het een werk om al die scans te verzamelen, fijn dat we het samen konden uitzoeken. Mattijs, jou wil ik bedanken voor het intekenen van de laesies en je hulp bij de analyses.

Dr. Di Russo, Prof. Dr. Spinelli, Marika, Federico and Rinaldo, thank you for your hospitality during my visit in Rome.

Prof. Dr. Dijkhuizen, Prof. Dr. Kappelle, Prof. Dr. van Heugten, Prof Dr. Geurts en Prof. Dr. Dijkerman, bedankt voor het lezen en beoordelen van mijn manuscript.

Daarnaast gaat ook veel dank uit naar mijn vrienden en familie. Allereerst dank aan enkele vrienden. Melle, voor onze waardevolle vriendschap. Marije K., voor je heerlijk originele kijk op de wereld. Bart, Gerrit, Jeroen, Maurice, Nina, Rasmus, Thomas, we go way back, en nog altijd maken jullie me aan het lachen. Bart, je geeft nog steeds fantastisch (bij)les. Aniek, Ellen, Jolanda, Mara, Marije, oftewel het 20e, jullie kennen mij beter dan ik zelf. Waar jullie het er jaren geleden al unaniem over eens waren dat ik dr. zou gaan worden wist ik zeker van niet. Dan moet ik bij deze toch mijn ongelijk toegeven… Jullie zijn een heerlijk cluppie!

Dan mijn familie; oma, ooms, tantes, neven, nichten en een snel groeiend aantal achterneefjes en nichtjes, ik heb er gelukkig te veel van om op te noemen. Ik waardeer de goede band die er als vanzelfsprekend is. In het bijzonder wil de buurtjes bedanken voor de alsmaar uitbreidende gezelligheid op de Zanddijk en jullie interesse in mijn promotietraject. Ook Rob, Gaby en Marlot, dank voor jullie gastvrijheid en interesse.

Lieve Hanna, zus en paranimf, het zal wel genetisch zijn, dat promoveren. Wellicht dat we ooit nog samen een artikel gaan schrijven. Ik hoop nog vele gesprekken met je te voeren over schrijven, programmeren en de wondere wereld van onderzoek doen. Je bent een bijzondere zus waar je op kunt bouwen. Koos, bedankt voor je altijd oprechte belangstelling. Lieve Alma, je bent met stip op één mijn lievelingsnichtje (en dat komt niet alleen omdat je mijn naam kunt zeggen).

Lieve papa, wat had ik je hier graag bij gehad. Ik mis je.

Lieve mama, dr. Simmes. Nog maar een paar jaar geleden verdedigde je je eigen proefschrift, een mooier voorbeeld kan ik niet hebben. Het is fijn om een moeder te hebben die begrijpt waar je mee bezig bent en daar oprechte interesse in heeft. Ik wil je bedanken voor de mooie basis die jij en papa me hebben gegeven in dit leven. Je bent een fantastische moeder en je staat altijd voor me klaar. Op naar nog vele wandelingen en weekendjes weg samen!

Lieve Niels, wat ben ik gek op je! Jij hebt me altijd gesteund tijdens de weg die promoveren heet. Je vergeleek mijn struggles in het onderzoek soms met het creatieve proces vanuit je eigen werk, waarmee je me nuttig advies kon geven. Waar je me kon helpen deed je dat: je speelde voor proefkonijn, hielp met het maken van figuren, maakte een video over mijn onderzoek en ontwierp de voorkant van dit proefschrift. Maar boven alles luisterde je elke dag weer geduldig naar wat ik dan ook te vertellen had. Je bent mijn allerliefste maatje, ik hou van je!

About the author

Curriculum vitae

Teuni ten Brink werd op 31 mei 1988 geboren in Nijmegen. In 2006 behaalde zij haar VWO diploma aan het Stedelijk Scholengemeenschap Nijmegen. Na een tussenjaar aan de *Vrije* Hogeschool in Driebergen volgde zij de bachelor Psychologie (studiepad Neuropsychologie) aan de Universiteit van Utrecht. Zij nam tevens deel aan de honours-minor van deze opleiding; het Von Humboldt College. Daarnaast heeft ze in 2009-2010 een bestuursjaar gedaan bij de Utrechtse Faculteitsvereniging der Sociale Wetenschappen "Alcmaeon". In 2013 behaalde zij een mastertitel in Neuropsychologie en in 2014 een mastertitel in Neuroscience & Cognition, beide aan de Universiteit van Utrecht. Gesuperviseerd door dr. Stefan Van der Stigchel en dr. Tanja Nijboer schreef zij haar masterthesis over hemianopsie, en later neglect. In 2014 startte zij haar promotieonderzoek binnen het Kenniscentrum Revalidatiegeneeskunde Utrecht onder begeleiding van prof. dr. Anne Visser-Meily en dr. Tanja Nijboer. In haar laatste jaar heeft zij onderzoekservaring opgedaan bij de Santa Lucia Foundation in Rome, onder leiding van dr. Francesco di Russo. Op dit moment is zij postdoc onderzoeker in het lab van dr. Stefan Van der Stigchel en docent aan de Universiteit van Utrecht binnen de afdeling Psychologische Functieleer.

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Brain Center
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ISBN 978-94-6299-829-2